Ethical Considerations for Deep Brain Stimulation and Other Invasive Neurotechnological Trials in People with Alzheimer's Disease

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Declaration of Originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief, no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Abstract

Alzheimer's disease is the leading cause of dementia worldwide, affecting more than 30 million people. FDA-approved drugs only provide temporary relief to memory problems, and no disease-modifying therapies are currently available. As such, different therapeutic modalities are being investigated to address the biological and/or cognitive manifestations of the disease. A number of these therapies are highly invasive and require stereotactic surgery, potentially posing a greater risk of harms to a vulnerable population with cognitive deficits that limit their ability to provide fully informed consent. Using an interdisciplinary and pragmatic approach to bioethical inquiry, this dissertation examines studies on deep brain stimulation in people with Alzheimer's disease, reviewing clinical trials and relevant animal studies to highlight pressing ethical concerns that ongoing and forthcoming trials need to address. By having three major publications during the course of the PhD as the main chapters, this thesis aims to enumerate ethical issues that encompass the genetic, neurobiological, cognitive, individual, and societal dimensions of deep brain stimulation for Alzheimer's disease. These ethical considerations can then be extended into other forms of novel neurosurgical trials such as cell implantation and gene therapy. Finally, this thesis incorporates other publications during the PhD to illustrate further conundrums on the use of deep brain stimulation and highlight directions for future bioethics research on the use of invasive neurotechnologies for dementia in terms of the importance of genetic underpinnings, clinical translation issues, communication of research objectives, media portrayal, and implications on criminal responsibility.

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"We are like dwarfs sitting on the shoulders of giants. We see more, and things that are more distant, than they did, not because our sight is superior or because we are taller than they, but because they raise us up, and by their great stature add to ours."

Originally stated by the philosopher Bernard of Chartres and affirmed by John of Salisbury in his 12th century writing (John of Salisbury 1955), this quotation has been re-formulated and made famous by the astrophysicist Sir Isaac Newton (Fawcett, Holloway & Rhynas 2015). Truly, this work would not have been possible without the intellectual giants who provided the baseline ethical reflection and scientific exploration drawn upon in writing this manuscript. What ensues is not for them though, for they are already gratefully acknowledged in the References. Instead, this section is dedicated to the other giants who have provided me with the trust, guidance, financial resources, material and emotional support, intellectual training, and inspiration to undertake three years of neuroethics research, publish several papers, and synthesise their main points into one big dissertation. These giants just did not raise me up to see the brain both within and beyond, but they also served as shoulders for me to stand on, lean on, and even cry on in this three-year pursuit of knowledge, wisdom, and enlightenment.

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Although I am the writer of this PhD dissertation and the main or a co-author of the publications included in it (my appreciation goes to all my collaborators and co-authors), this body of work would have never materialized without the help, support, mentorship, trust, and encouragement of several institutions and individuals. I may not have been able to mention all the people I have met during this journey from whom I learned much, but my gratitude surely extends far and deep. Hopefully, I could continue growing as a researcher and as a person, and perhaps one day, also be tall enough to support and uplift other individuals in their pursuit of knowledge and of the untarnished truth.

Table of Contents

Abbreviations and/or Acronyms

Abbreviation/Acronym	Meaning
AAAS	The American Association for the Advancement of Science
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive subscale
BBP	Blue Brain Project
BD	Bipolar disorder
CSF	Cerebrospinal fluid
DBS	Deep brain stimulation
dNF	Decoded neurofeedback
EOAD	Early-onset Alzheimer's disease
EPSP	Excitatory postsynaptic potential
FAD	Familial Alzheimer's disease
FDG	[^{18}F] fluorodeoxyglucose
FTD	Frontotemporal dementia
GWAS	Genome-wide association studies
HBP	Human Brain Project
HDE	Humanitarian device exemption
HFS	High frequency stimulation
HGP	Human Genome Project
hUBC-MSCs	Human umbilical cord blood mesenchymal stem cells
IBRO	International Brain Research Organization
INS	International Neuroethics Society

IPSP	Inhibitory postsynaptic potential
MCI	Mild cognitive impairment
MDD	Major depressive disorder
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cells
NBM	Nucleus basalis of Meynert
OPC	Open peer commentary
PD	Parkinson's disease
PET	Positron emission tomography
PIAAAS	Personality, identity, agency, authenticity, autonomy, and/or self
PiB-PET	^{11}C-labeled Pittsburgh compound B (PiB) positron emission tomography
rtfMRI-NF	Real-time fMRI (functional magnetic resonance imaging) neurofeedback
S-IADL	Seoul instrumental activities of daily living
SfN	Society for Neuroscience

List of Publications

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SECTION I.

INTRODUCTION

Chapter One. Introduction: Neuroethical Considerations for Emerging Neurotechnologies

Neuroethics, a discipline encompassing both the ethics of neuroscience and neuroscience of ethics (Roskies 2002), has gained prominence in the past decade and a half, as evidenced by an increase in publications and research efforts and by the establishment of dedicated journals and academic societies (Racine et al. 2017; The Lancet Neurology 2018). Among the key concerns of neuroethics is the investigation of ethical issues associated with novel technologies for people with neurologic or psychiatric conditions. Although ethical concerns on bio- and neurotechnologies (Twiss 1976; Siegfried, Lazorthes & Sedan 1980; Kletzel, Morgan & Frader 1998; Ryan 2000) and on on-going practices and research involving the management and treatment of psychiatric and neurologic disorders (Redlich & Mollica 1976; Dickens 1981; The American Academy of Neurology Ethics and Humanities Subcommittee 1996; The Ethics and Humanities Subcommittee of the American Academy of Neurology 1998) have been raised before the formalization of neuroethics as a discipline and the establishment of dedicated societies and journals (Buniak, Darragh & Giordano 2014), the creation of a more formal field of inquiry has led to more unified, better funded, and interdisciplinary research efforts and to a stronger push to integrate ethical inquiry into neuroscience research and neurotechnology development (Martin et al. 2016; Becker et al. 2017), especially for those targeting vulnerable populations (Singh 2013; Stevenson et al. 2013; Fins 2016).

This thesis draws upon the interdisciplinary nature of neuroethical inquiry to dissect a broad range of ethical issues associated with clinical trials on invasive neurotechnologies for Alzheimer's disease (AD). By focusing on deep brain stimulation (DBS) trials, this thesis

highlights concerns starting from the translational value of pre-clinical studies in different animal models (Viaña et al. 2017) to the design of clinical trials to account for population-specific characteristics that might influence disease progression and intervention response (Viaña, Bittlinger & Gilbert 2017). This thesis also aims to underscore the importance of acknowledging that trial participants are persons with a selfhood that has already been influenced by the disease, and as such, the impact of an invasive intervention such as DBS on their identity, self-image, self-appraisal, and relationality must be given importance equal to that of cognitive and neurologic outcomes (Viaña & Gilbert 2018). By taking an interdisciplinary approach, as reflected in the three major papers that comprise this thesis (Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018; Viaña et al. 2017), this study aims to highlight that both AD and DBS have effects not only on the brain (cognition and behaviour), but also on the person as an embodied whole and as a relational being in a society and a particular culture that also has its views on an AD diagnosis and on recipients of a particular intervention such as DBS.

In addition to taking an interdisciplinary lens, this thesis also utilises an empirical, applied, and pragmatic bioethical approach (Fins, Miller & Bacchetta 1997, 1998; Racine 2008a, 2008b). Pragmatism, a philosophical tradition that originated from the USA around 1870 and initially forwarded by Charles Sanders Peirce, William James, and John Dewey, emphasises the clarification of the contents of hypotheses by tracing their practical consequences or implications for what we will or should do (Hookway 2016). The version of pragmatism in bioethics that is applied in this work draws upon from the moderate natural pragmatism forwarded by Eric Racine (2008b, 2013) and the clinical pragmatism method proposed by Joseph Fins, Matthew D. Bacchetta, and Franklin G. Miller (1997, 1998), both of

which were mainly or partly inspired by John Dewey's formulation of pragmatism, which emphasises that moral problem solving should be based on the experimental method of inquiry (Fins, Bacchetta & Miller 1997). Dewey's naturalistic metaethics of value judgements, grounded in developmental and social psychology, argues the use of reflective intelligence in revising our judgements in light of the consequences brought about by acting on them, allowing redirection of conduct when habits fail. Through an experimental method of inquiry, value judgements are tested by putting them into practice and assessing whether the results are satisfactory in the way they solve problems while limiting side effects to an acceptable level, enable successful outcomes to new problems, and provide satisfactory results when compared to alternative value judgements. Dewey's ethics distinguishes itself by focusing on human conduct as warrant for value judgements, rather than on a fixed reference point such as Platonic Forms, God's command, nature, or pure reason (Anderson 2018).

Racine's (2013) reading of Dewey's (1922) pragmatism highlights his view of pragmatism as an approach that stresses how ethical behaviour and thinking are contextual. Racine compares it with Beauchamp's and Childress's principlism (2009), and emphasises how pragmatism reflects more on aspects of social justice, empirical research's transformative role, and institutional and macro-level changes on health policy due to the influence of democracy and deliberation in the construction of shared common goods (Racine 2013). Furthermore, his perspective on pragmatism emphasises the positive contribution of science to debates on ethics and policy but also challenges various forms of foundationalism in philosophy and science. In addition to Dewey's (1922) pragmatism, Racine (2008b) has also drawn upon the work of various philosophers such as Van Rensselaer Potter on bioethics being the bridge between science and the humanities; Anne Fagot-Largeault on the auto-regulation process

that is based on social adaptation in bioethics; and Jonathan Moreno on pragmatism's rejection of fundamental ethical principles that rely on *a priory* inquiry. By using ideas from various pragmatists, Racine (2008b) then proposes that a moderate pragmatic naturalism best describes the state bioethics has taken in order to respond to new healthcare situations and scientific advances. The theoretical commitments of Racine's (2008b) moderate pragmatic naturalism are:

> "1) Distinction between 'is' and 'ought' granted with qualifications; 2) Ethical predicates are properties that cannot be reduced to natural properties but are best understood within a fact-value continuum; 3) Empirical knowledge does not bring ethical justification of ethical norms but ethical knowledge must take into account human capacities. 'Is' does not imply 'ought' but 'ought' implies 'can'; 4) Ethical norms are not natural laws but norms and rules proper to human social life. There are no natural moral laws but moral rules can be better understood from a factual point of view that takes into consideration constraints to moral agency; 5) Ethical norms do not simply follow from reason or experience but from their interaction, e.g. reflexive equilibrium; 6) Bioethics is neither autonomous nor heteronomous but best described as an interdisciplinary field with practical goals such as creating new forms of wisdom in the delivery of healthcare and the pursuit of health; 7) Normative ethics is normative. Metaethics is both empirical and conceptual." (p. 98, Racine 2008b)

Racine (2008b) forwards that moderate natural pragmatism "expresses some of the commitments required for the flourishing of new forms of wisdom for the delivery of healthcare and the pursuit of health" (p. 100, Racine 2008b). Through the lens of pragmatist bioethics, Racine has advocated for the acknowledgement of pluralism in neuroethics and for more active involvement of physicians, allied healthcare personnel, and stakeholders in

improving healthcare (Racine 2008a). He has also used this framework to investigate the effect of media depictions of disorders of consciousness on public perceptions on disorder prognosis; the differing opinions of physicians, and the contextual and personal factors influencing such, on the prognosis of people with disorders of consciousness (Racine 2008b); and the reason for ongoing controversies on death determination and why lay and foundational expert views need to co-evolve in order to reconstruct the meaning of death considering its practical importance (Racine 2015).

Another perspective greatly inspired by Dewey's (1922) pragmatism is that of Fins, Bacchetta, and Miller (1997, 1998), who proposed clinical pragmatism as a method of problem solving. The goal of clinical pragmatism is to reach consensus on good outcomes in real clinical cases posing moral problems. This is achieved by a thorough process of inquiry, discussion, negotiation, and reflective evaluation, treating moral rules and principles as hypothetical guides for conduct rather than as fixed and absolute moral laws (Fins, Bacchetta & Miller 1997). In clinical pragmatism, health practitioners engage in a collaborative process of problem solving when they

> "(1) assess the patient's medical condition; (2) determine and clarify the clinical diagnosis; (3) assess the patient's decision-making capacity, beliefs, values, preferences, and needs; (4) consider family dynamics and the impact of care on family members and others intimately concerned with the patient's well-being; (5) consider institutional arrangements and broader social norms that may influence patient care; (6) identify the range of moral considerations relevant to the case in a manner analogous to the clinical process of differential diagnosis; (7) suggest provisional goals of care and offer a plan of action including plausible treatment and care options; (8)

negotiate an ethically acceptable plan of action; (9) implement the agreed upon plan; (10) evaluate the results of the intervention; and (11) undertake periodic review and modify the course of action as the case evolves" (p. 131, Fins, Bacchetta & Miller)

Ultimately, clinical pragmatism focuses on the interpersonal process of moral problem solving, and as such, it requires being able to take others' perspectives, engage in deliberative dialogue, and negotiate questions of meaning and the goals of care to reach an informed and inclusive consensus (Fins, Bacchetta & Miller 1997, 1998). Using the case of a person with Parkinson's disease who became non-arousable due to a yeast infection, has poor prognosis, and who has a wife who wanted him to receive all aggressive measures including cardiopulmonary resuscitation, Fins, Bacchetta, and Miller (1997) illustrated how clinical pragmatism can be used by the physician to undertake authentic communication with the wife and achieve consensual decision on the appropriate therapeutic course at the end of life, taking into account situational, relational, institutional, social, religious, and cultural factors influencing decision making (Fins, Bacchetta & Miller 1997). Clinical pragmatism has also been used by Fins (2005) to identify challenges in the care of patients with severe brain injury and on ways in which a proper plan of palliative care can be negotiated with surrogates, considering medical facts and the values of the patient and surrogates while ensuring balance between burdens and benefits.

Although pragmatism in bioethics focuses more on a deliberative and dynamic approach to decision-making rather than on the direct top-down application of bioethical principles and moral laws (Fins, Bacchetta & Miller 1997; Racine 2008b), certain moral rules, principles, and guidelines can still be used as hypotheses or as available frameworks for analysing moral situations (Arras 2002) and determining the most appropriate ethical course

of action in a particular context. In this thesis, principles from various guidelines such as the Nuremberg Code, Declaration of Helsinki, Belmont Report, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects are used to evaluate clinical trials on their social or scientific value, scientific validity, subject selection, risk-benefit ratio, study design, informed consent procedure, communication of research results, and treatment of participants (Emanuel, Wendler & Grady 2000; Li et al. 2016). Although not explicitly stated all the time, the ethical considerations forwarded throughout this dissertation are also guided by the four key principles in medical ethics, which are respect for autonomy, beneficence, non-maleficence, and justice (Beauchamp & Childress 2013). The application of a pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) means that no principle takes precedence or priority over the others; rather, these principles are just used as guides to determine the most appropriate course of action to protect and promote the welfare of research participants and other stakeholders, taking into account scientific and medical knowledge, relational and social dimensions of living with AD and/or receiving an invasive intervention such as DBS, and the context in which the trial is performed and where decisions are made. By utilising a pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) guided by cornerstone ethical guidelines and medical ethics principles to evaluate different aspects of a clinical trial (Emanuel, Wendler & Grady 2000; Li et al. 2016), this dissertation and the publications in it emulate the clinical and research ethics-grounded analysis performed by Issa and Keyserlingk (2000), Karlawish and Casarett (2001), Karlawish and Clark (2002), Beattie (2007), and Fisk (2007) to dissect ethical issues in research involving people with dementia and by Cabrera, Evans, and Hamilton (2014), Clausen (2010), and Racine, Bell, and Zizzo (2014) to determine ethical considerations on the expanding use of DBS.

It is important to acknowledge that the experimental method championed by pragmatism also has its challenges, particularly in determining whether the tested principles provide the necessary guidance to a situation and lead to desired consequences. Although, consensus can be viewed as a potential way of determining the success of a tested principle, the influence of inequalities in power, wealth, and information should not be disregarded (Arras 2002) as this could easily degenerate pragmatism into clinical manipulation and become a way for the physician to reassert paternalism (Tong 1997). Nonetheless, considering pragmatism's (Fins, Bacchetta & Miller 1997; Racine 2008b) dynamism, self-reflexivity, and fluidity and its commitment to modest fallibilism (Arras 2002), this approach provides adequate opportunity for self-correction (Brown 2008) should initial consensus prove to exacerbate rather than ameliorate paternalistic attitudes and undermine patient autonomy. Furthermore, even though consensus cannot be achieved, an open and honest discussion and deliberation could still result to the goods of mutual respect and trust between participants and health professionals (Tong 1997). Pragmatism's acknowledgement of fallibilism in a sense that knowledge is not absolute and in the restriction of cognitive claims in a fluxative world (Brown 2008) could also provide opportunity for speculation, provided that speculations follow from a thorough review of scientific, clinical, narrative, and contextual information relevant to the case (Fins, Bacchetta & Miller 1997; Fins 2005). By employing a rigorous method in reaching an ethics differential diagnosis or speculations on relevant moral considerations, a better negotiated and workable consensus on care plans with the patient and family could be achieved (Fins 2005), in addition to tempering assertions and preventing ideological distortions (Fins 2008) in bioethical reflections concerning clinical and/or research scenarios.

Through the principle-guided pragmatic approach (Fins, Bacchetta & Miller 1997; Emanuel, Wendler & Grady 2000; Racine 2008b; Li et al. 2016) described in the preceding paragraphs, this dissertation critically examines the protocols of animal research and in-human trials of DBS for AD, determines aspects of these studies that necessitate ethical reflection, and provides recommendations that directly address ethical concerns arising from the recruitment, design, and conduct of these studies. Considering the emphasis placed by pragmatism on the contribution of scientific and clinical knowledge derived from empirical investigations to ethical debates (Fins, Bacchetta & Miller 1997; Racine 2008b), ethical reflection was based on the set-up and results of clinical trials and/or animal studies testing the effect of DBS on animal models or on people with AD. For the three publications that are the main focus of this dissertation (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018), past and ongoing trials of DBS in people with AD were determined using a PubMed and clinicaltrials.gov search of the keywords "DBS Alzheimer's disease" while completed animal studies that employed DBS of the fornix were identified using the keywords "DBS fornix" on PubMed. For the paper examining potential effects of DBS on the selfhood of people with AD (Viaña & Gilbert 2018), references were obtained through a search on PubMed, Scopus, and Google Scholar using the keywords "Alzheimer's disease", "dementia", "deep brain stimulation", "selfhood", "social constructionist", and "identity" and their corresponding permutations and combinations. Primary studies and case reports that explored the impact of AD on the social constructionist framework's three aspects of the self were identified and highlighted in this review. There were no studies that investigated the impact of DBS on selfhood using the social constructionist framework, so relevant studies that discussed its effects on self recognition and perception, psychological and psychiatric profiles, identity, and social adjustment were referenced instead. For the research involved in all three

publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018), the references of highly relevant articles were also examined to expand the search coverage and identify other articles related to the initial keywords used. No specific period was set during the searches, and only articles that are fully in or with abstracts in English were included as references for the three publications.

For the three main publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018), the pragmatic analytical framework (Fins, Bacchetta & Miller 1997; Racine 2008b) was employed to provide recommendations that acknowledge and address ethical concerns specifically arising from evaluating the safety and efficacy of DBS in people with AD. After obtaining relevant literature through methods detailed in the preceding paragraph, scientific papers describing the clinical trials of DBS for people with AD were carefully and critically read and details on different aspects of the trial such as inclusion and exclusion criteria, consent procedure, characteristics of the population enrolled, study design, and measured outcomes and results were placed in a Microsoft Excel matrix to facilitate better comparison among different trials. By using information on the pathophysiology, diagnosis, and prognosis (Fins, Bacchetta & Miller 1997) of AD and the mechanisms of action and possible risks of DBS, better assessment of the suitability of the enrolled participants and the design of the clinical trials could be made. With the focus of clinical pragmatism on patient's decision-making capacity and family dynamics (Fins, Bacchetta & Miller 1997), the way the informed consent was obtained for the trials and how the opinions of family members and caregivers were taken into account in the consent procedure, in addition to how AD could affect decision-making capacity, were also examined. In the identification of ethical considerations in the three major publications, institutional arrangements and

broader social norms (Fins, Bacchetta & Miller 1997) were considered in identifying DBS access issues and in determining how social factors such as malignant positioning of people with dementia (Sabat & Collins 1999) and therapeutic misconception of invasive neurotechnological trial participation (Fisher et al. 2012) could affect the lived experience of a person with dementia who is receiving DBS. Furthermore, relevant moral considerations are also identified (Fins, Bacchetta & Miller 1997), highlighting potential tensions between the need to properly and systematically investigate an intervention that might be beneficial to people with AD and the obligation to ensure that vulnerable people with impaired-decision making are not taken advantage of and are not subjected to risky interventions with minimal possibility of benefit. With the focus of pragmatic ethics on suggesting goals of care (Fins, Bacchetta & Miller 1997) and on drawing from various disciplines to create new forms of wisdom in the pursuit of health (Racine 2008b), the ultimate aim of the three main publications in this dissertation (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) is to suggest plans of action that would minimise harm and ensure the welfare of clinical trial participants, ensuring that adequate care and respect are provided in the context of a clinical trial. Finally, clinical pragmatism advocates for periodic review and modification of course of action as the case evolves (Fins, Bacchetta & Miller 1997). As such, results from previous clinical trials of DBS for AD are also assessed to see how they can inform the design of ongoing and planned trials, ensuring that the participants enrolled and that the set-up of the clinical trials would lead to the greatest prospect of benefit and the least possibility of undue medical and social harms.

At this point, it is also important to stress what this dissertation does not try to achieve. First, although pragmatic ethics focuses on the role of deliberation and negotiation (Fins,

Bacchetta & Miller 1997; Racine 2008b), research for this dissertation does not include direct engagement with people participating in DBS for AD clinical trials, their family members and/or caregivers, and researchers and clinicians having an active role in the conduct of these trials, given that none of the trials are performed in Australia. As such, this dissertation employs a relatively limited pragmatic approach. Nevertheless, by drawing directly from information on how the trials are set-up and recruited, in addition to previous studies on clinical trials of DBS for other indications and on how Alzheimer's disease could affect selfhood and decision-making, this thesis embraces the pragmatic framework, at least to the extent in which it uses an interdisciplinary approach that acknowledges the contributions of medicine, social science, and philosophy to providing practical recommendations that would help guide the ethical conduct of ongoing and prospective DBS for AD trials. The three main publications in this thesis (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) could also serve as groundwork for future ethics research that employ a fuller pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) – directly engaging with participants and researchers in DBS for AD trials, determining how the recommendations forwarded in the publications help improve the conduct of these trials, and gauging additional concerns of multiple stakeholders that warrant further moral reflection.

Second, though some philosophical viewpoints are raised, particularly in Chapters 3 and 6, the primary goal of this thesis is neither to extensively review and/or engage with these discussions nor to provide an in-depth philosophical and conceptual analysis on how DBS and/or AD impact philosophical conceptions of mind, personhood, selfhood, and identity. Instead, this work aims to directly engage with researchers, clinicians, and people attending to those with AD, via the three main publications highlighted in this dissertation, which were

also published in journals ranked by Scimago Lab to be in the first quartile of their respective subjects (Scimago Lab 2017). To better achieve the practical goals of this thesis, it is urgent that ethical recommendations directly addressing the trials are forwarded, formulated and published in medically-oriented journals, especially ones that focus on dementia, to best attract the attention of clinicians, researchers, and promote the interests of people with AD who are already participating or who are planning to participate in trials of DBS or other invasive neurotechnologies.

The next paragraphs in this Introduction section provide brief descriptions of the remaining sections in this dissertation to give readers an idea of the overall flow of the thesis and how the three main publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) and other publications during my PhD are integrated into the overall narrative.

To facilitate a more fluid discussion of ideas and to attract a wider readership before the presentation of the three main peer-reviewed publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) as three separate chapters, following the Introduction section are descriptive introductory chapters on AD (Chapter 2) and DBS (Chapter 3). Similar to introductory sections in scientific and social science publications, the main aim of Chapters 2 and 3 is to provide readers of the three main publications in Chapters 4, 5, and 6 sufficient background information on the science behind DBS and AD and a brief overview on some of the sociological, psychological, and philosophical discussions on their implications on selfhood and identity. These two chapters neither aim to appraise the positions or conclusions of the literature presented nor argue for or against them, for they

are engaged with in the incorporated (for Chapter 3) and ensuing publications (Chapters 4, 5, and 6).

Following this chapter (Chapter 1: Introduction), Part 1 of Chapter 2 provides a succinct overview on the biology of AD; while Part 2 briefly introduces how the disease can affect the selfhood of people with AD, providing a concise introduction of different perspectives and approaches used to investigate AD-associated changes in selfhood and identity. Initial information provided in Part 2 of Chapter 2 serves as a prelude to the main discussion in Chapter 6 on the possible effects of DBS on the selfhood of people with AD.

Chapter 3 then introduces DBS, providing a brief history and information on its possible modes of action. This chapter also includes three publications that this dissertation's author has contributed to, two of which highlight the ethical dimensions of this technology and concerns that extend beyond its neurobiological mechanism and intended effects on a particular disorder (such as motor improvement for people with Parkinson's disease). The first paper entitled "I miss being me: phenomenological effects of deep brain stimulation", published in the American Journal of Bioethics Neuroscience, illustrates the perspectives of people with PD who received DBS, focusing on how the intervention led to self-estrangement and to whether such estrangement was deteriorative or restorative in nature (Gilbert et al. 2017). The second study entitled "A personal narrative on living and dealing with psychiatric symptoms after DBS surgery", published in Narrative Inquiry in Bioethics, provides a more in-depth and long-term investigation on one of the people with PD in the study of Gilbert et al. (2017) to illustrate the challenges that a DBS recipient may face as a result of DBS-associated psychological and psychiatric sequelae and to demonstrate how someone copes with and

integrates them into his/her self-image (Gilbert & Viaña 2018). These papers would bring into the spotlight ethical concerns regarding an invasive and risky intervention such as DBS that extend beyond its "initial" safety and clinical efficacy, most of which will also be touched on in the discussions on possible long-term, relational, and social effects of DBS in people with AD in Chapters 4 to 7. This chapter also introduces several philosophical reflections on the possible effects of DBS on selfhood and identity, a number of which will be drawn upon in Chapter 6. This chapter is concluded by a paper on "'Deflating the "DBS causes personality changes" bubble", published in Neuroethics, that cautions against ethics hype and encourages philosophical reflections to be grounded in clinical realities (Gilbert, Viaña & Ineichen 2018).

As mentioned earlier, this dissertation focuses on three main papers discussing different ethical issues on DBS for AD. Chapter 4 presents the paper entitled "Currents of memory: recent progress, translational challenges, and ethical considerations in fornix deep brain stimulation trials for Alzheimer's disease", published in Neurobiology of Aging, which summarizes different trials and animal studies on fornix DBS for AD and highlights associated translational, medical, and ethical issues (Viaña et al. 2017). Building on the discussion in Chapter 4, Chapter 5 narrows down the focus to a specific sub-population of people with AD who exhibit cognitive dysfunction earlier, have a more aggressive disease course, and interestingly, had a different response, when taken as a group, to fornix DBS in one of the clinical trials. This chapter, which is comprised of the paper entitled "Ethical considerations for deep brain stimulation trials in patients with early-onset Alzheimer's disease" published in the Journal of Alzheimer's Disease, underscores the importance of acknowledging that additional ethical issues might arise in specific participant sub-populations and details

additional ethical concerns that are raised by including participants with a particular genotype in DBS for AD studies (Viaña, Bittlinger & Gilbert 2017). Finally, Chapter 6 extends the discussion to the social psychology domain and uses this as a platform to frame the ethical discussion. The paper "Deep brain stimulation for people with Alzheimer's disease: anticipating potential effects on the tripartite self", which was published in Dementia, builds on Rom Harre's and Steve Sabat's tripartite model of selfhood to anticipate how DBS for AD might affect the selfhood of participants and what ethical considerations should be made to account for and address these effects, some of which could be unintended and potentially detrimental to the person with AD (Viaña & Gilbert 2018).

Chapter 7 brings together the ideas raised in the three main papers on DBS for AD and also integrates key points raised by the three papers in Chapter 3 on the ethics of DBS for PD. It synthesizes the main points in these publications and proposes a way to go forward for existing and future trials on DBS for AD. By including a poster presentation entitled "Ethical Considerations for Cell Implantation in Alzheimer's Disease" and an open peer commentary entitled "Of Meatballs and Invasive Neurotechnological Trials: Additional Considerations for Complex Clinical Decisions", indexed and published in the American Journal of Bioethics Neuroscience, this chapter also illustrates how the framework used to extract, explore, and elaborate on the ethical issues on DBS for AD can be extended to other neurotechnologies such as cell implantation and gene therapy, both of which have been and are also currently being tested in people with AD. Although there are key differences among the three technologies, a number of the ethical issues are partially or fully translatable, and insights from the three main publications on DBS for AD can be used to further dissect ethical concerns

for cell implantation, gene therapy, and other invasive neurotechnologies being explored for and tested in people with AD.

Throughout my doctoral research, I have also contributed to and have written several open peer commentaries and full articles on a wide range of bio- and neuroethical topics. These OPCs and papers were published in AJOB Neuroscience and Bioethics. A number of the frameworks and methodologies used and arguments raised in these commentaries and papers can be used for further inquiry on the ethics of DBS and other invasive neurotechnologies for AD. As such, these papers are incorporated into Chapter 7 as directions for future research. In particular, this chapter includes articles on the value of findings from genome-wide association studies (Viaña, Bueno & Gilbert 2017), the portrayal of 3D bioprinting in the media (Gilbert et al. 2018), portrayal of the goals of the Human Brain Project (Viaña & Gilbert 2016), the influence of neurological findings on criminal culpability (Gilbert, Vranic & Viaña 2016), and ethical issues in the clinical translation of decoded neurofeedback (Viaña et al. 2016). The last part of Chapter 7 highlights key ideas, concepts, arguments, and/or research approaches in these studies and commentaries, and it also illustrates how they can be translated and applied to future neuroethical investigations on ethical conundrums on emerging neurotechnologies for people with AD.

Finally, Chapter 8 synthesizes information presented in the preceding chapters and summarises the key ideas presented in the publications included in this paper. It also reiterates the main objectives of the PhD project and concisely demonstrates how the three main publications in Chapters 4, 5, and 6 meet these objectives and how ideas raised and methods used in the remaining publications can be used as a platform to investigate

additional ethical concerns raised by other neurotechnologies and clinical trials for people with dementia. This chapter also includes a discussion of the major limitations of the research performed during the PhD and provides suggestions for future work to address and overcome these limitations.

Overall, this thesis aims to extend the discussion on ethical issues involved in the management and care of and research involving people with dementia (Strech et al. 2013; Pierce 2014; Johnson & Karlawish 2015; Ovadia & Bottini 2015; Forlini 2017; Robillard & Feng 2017; Siegel, Barrett & Bhati 2017; Robillard et al. 2018) and in the development and translation of emerging neurotechnologies. By focusing on DBS clinical trials for people with AD, it emphasizes the need to develop specific ethical recommendations for newly-developed technologies or when extending the applications of or introducing modifications to existing ones. Although this thesis acknowledges the usefulness of existing ethical publications (Pierce 2014; Ovadia & Bottini 2015; Siegel, Barrett & Bhati 2017; Bittlinger & Müller 2018) and even recommends extending the ethical frameworks and ideas raised in them to other technologies for dementia, it also aims to underscore the importance of accounting for nuances in medical details and social context, and adapting, reconciling, and/or reframing ethical discussions and recommendations to accommodate these specificities and differences, as in the case of DBS for people with early-onset AD. In no way this study exhausts all the ethical issues on DBS for AD; surely, new findings from forthcoming clinical trials or modifications to the technology would necessitate additional ethical reflection. Hopefully, this study could serve as a stepping stone to guide and encourage further ethical exploration on this topic.

Truly, rapid progress in neuroscience has encouraged the firm and formal establishment of neuroethics as a research discipline. It is expected that with the further development of new neurotechnologies and the exploration of new indications for existing ones, neuroethics will play a pivotal role in ensuring the ethical, humane, and just evaluation and translation of these technologies to the populations who need them the most. With different scholars from a wide range of backgrounds and academic disciplines contributing to the neuroethical discussion, neuroethics is poised to demonstrate how a collaborative and multi-faceted research endeavour would benefit the medical and research enterprise while ensuring that the most important stakeholders, recipients of the developed technologies, are put on the pedestal. Hopefully, this thesis illustrates the result of an interdisciplinary mode of inquiry in the way that it viewed the ethics of DBS for AD from neuroscientific, medical, psychological, sociological, and philosophical vantage points. It also demonstrates how this interdisciplinary and pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) could facilitate an ethical discussion that acknowledges the scientific and medical dimensions of a disorder and an intervention while putting equal importance to the lived experience and social positioning of people living with AD and participating in a DBS clinical trial.

SECTION II.

Descriptive Literature Review

Chapter Two. The Brain and the Self in Alzheimer's Disease

Chapter 2 is divided into two parts, with the first part reviewing the neuroscience of AD and the second part reviewing discussions on how AD could affect selfhood and identity. Specifically, Part 1 of Chapter 2 reviews literature on the prevalence, diagnosis, genetics, pathophysiology, and pharmacologic management of AD and therapeutic modalities that are being explored to address its symptoms. Its main goal is to familiarise readers with the neurobiology of AD, which would be useful in understanding scientific, medical, and ethical points raised in Chapters 4 (Viaña et al. 2017), 5 (Viaña, Bittlinger & Gilbert 2017), and 6 (Viaña & Gilbert 2018). Part 2 of Chapter 2 then provides a descriptive overview of different frameworks used to investigate AD-associated changes in selfhood and identity and of results from empirical studies utilising these frameworks. This overview would help readers better follow the arguments forwarded in Chapter 6 (Viaña & Gilbert 2018), which hypothesises possible effects of DBS on the selfhood of people with AD and their implications on informed consent, study design, and treatment of study participants.

Part 1: Alzheimer's Disease: A Neurobiological Overview

I. Prevalence and Cost of Dementia and Alzheimer's Disease

Dementia affects an estimated 50 million people worldwide, with nearly 10 million new cases recorded each year (World Health Organization 2017). It also has a total estimated worldwide cost of US$ 818 billion (Prince et al. 2015). In Australia, 425,416 people live with

dementia, which was estimated to cost the country more than 15 billion AUD in 2018 (Dementia Australia 2018).

Alzheimer's disease (AD) is the most common form of dementia, accounting for approximately 69.9% of all dementia cases (Plassman et al. 2007) or almost 5.3 million people in the USA alone (Alzheimer's Association 2015), with 5.1 million of patients aged 65 and above (Hebert et al. 2013). Considering the number of people in Australia with dementia, it is estimated that around 297,366 Australians have AD (Plassman et al. 2007; Dementia Australia 2018).

The burden of dementia on individuals, their family, and society raises salient concerns on the allocation of limited health resources and in the setting of priorities for medical research and treatment development. Should more priority be given to dementia, a condition that primarily affects older individuals, over conditions that affect children or people in mid-age (Clark 1985)? Would it be justifiable to allocate limited resources to curing or reversing a disease and prolonging life in a population that in general, is expected to experience hardship due to other health problems and potential rejection or stigmatisation by younger individuals (Mahendra 1984)? Finally, is it appropriate to utilise costly high-tech applications to meet the care demands and reduce disease burden of older populations (Clark 1985)? Although this thesis does not aim to extensively reflect on the issue of justice with regards to funding allocation for research and healthcare of geriatric populations, especially of those with dementia, the paper in Chapter 4 (Viaña et al. 2017) provides an overview of societal issues arising in the development and application of fornix DBS in people with AD.

II. Clinical Diagnosis of Alzheimer's Disease

The proper diagnosis of AD is crucial in disease management and in the development and testing of new interventions, particularly those aimed at addressing the core symptoms and neuropathology of AD. Misdiagnosis is linked to many ethical issues. Misdiagnosis could lead to the prescription of unnecessary medications (Gaugler et al. 2013) and exposure to their potential adverse side effects (Kerchner, Tartaglia & Boxer 2011). Furthermore, misdiagnosis in people who are subsequently recruited into a clinical trial could lead to iatrogenic harms in the absence of a foreseeable benefit, especially for trials targeting pathologies specific to Alzheimer's disease and/or requiring an invasive procedure. Finally, false positives could create unnecessary distress to the individual and to his or her family while false negatives could create a false sense of security and delay the initiation of therapies that could delay the onset of cognitive symptoms and improve quality of life (Howe 2006).

Full diagnosis of AD is established by neuropathologic findings of amyloid beta (Aβ) plaques and neurofibrillary tangles, whereas its clinical diagnosis is mainly based on slowly progressive dementia and gross cerebral cortical atrophy observed through neuroimaging (Bird 1998). Conventionally, clinical diagnosis of AD is based on criteria set by the National Institute of Neurological and Communicative Disorders (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ARDRA) (McKhann et al. 1984); however, in 2011, the National Institute on Aging (NIA) and the Alzheimer Association published three reports that suggested criteria for the asymptomatic preclinical, pre-dementia, and dementia phases of AD (Jack et al. 2011; illustrated in Figure 1).

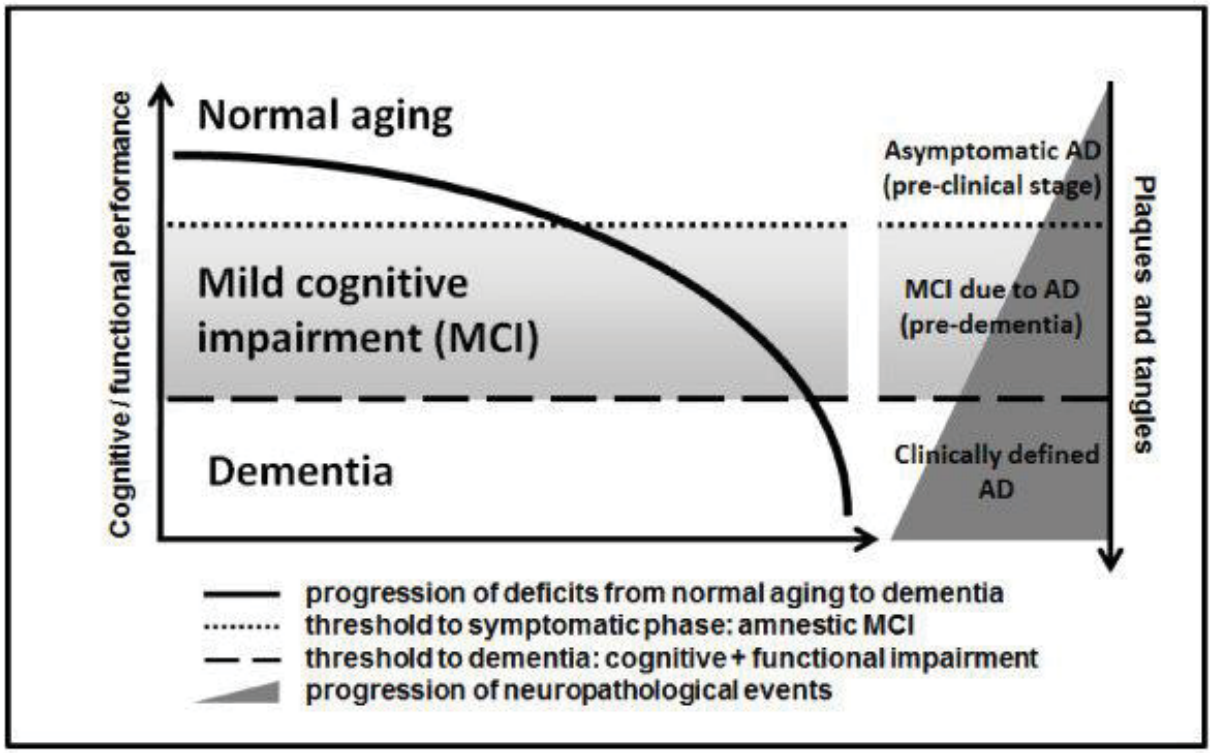

Figure 1. Different phases of Alzheimer's disease (figure from Forlenza, Diniz & Gattaz 2010; available via CC BY 4.0 license, https://creativecommons.org/licenses/by/4.0/). It is important to note that not all people with MCI (mild cognitive impairment) will progress to clinically-defined AD dementia (Frolich et al. 2017).

Although mainly intended for research purposes, the pre-clinical phase of AD proposed by Sperling et al. (2011) is characterised by people starting to exhibit amyloidosis and neurodegeneration as observed from PET and fMRI scans and from CSF measurements of low $A\beta_{142}$ levels and high tau/p-tau ratio. Subtle changes in baseline cognition and poor performance on more challenging tests, which are not substantial for Mild Cognitive Impairment (MCI) diagnosis, are also observed.

The pre-dementia phase of AD is clinically defined by reports from the person or clinician regarding declining cognition and impairment in one or more cognitive domains, indicated by scores on cognitive tests 1 to 1.5 standard deviations below the mean for their

age and education-matched peers. These people still preserve independence in functional abilities and are not significantly impaired in social or cognitive functioning. Ruling out other sources of cognitive decline, providing evidence of longitudinal decline in condition, and having history consistent with AD-associated genetic factors further provide evidence for diagnosing MCI consistent with AD pathophysiology. Moreover, biomarkers of Aβ deposition, neuronal injury, inflammation, oxidative stress, synaptic damage, and neurodegeneration could provide support that the observed cognitive impairment is due to AD pathology; however, their use at this stage is mainly limited to research and clinical trial settings (Albert et al. 2011).

Lastly, the dementia phase of AD is defined as having cognitive or behavioural impairment in two or more domains, which includes memory, reasoning and executive function, visuospatial abilities, language functions, and personality, that significantly interferes with ability to function at work or at usual activities (McKhann et al. 2011). Aside from such impairments, people with AD dementia could also exhibit confusion, agitation, withdrawal, and hallucinations, and some could also occasionally experience seizures, Parkinsonian features, mutism, myoclonus, increased muscle tone, and incontinence. Death from people with AD dementia usually result from general inanition, malnutrition, and pneumonia (Bird 1998).

AD dementia can be clinically classified as either probable or possible AD dementia. Probable AD dementia is mainly characterized by an insidious onset evident from a clear-cut history of cognitive worsening and is not due to cerebrovascular disease or other forms of dementia. On the other hand, possible AD dementia has an atypical course with sudden onset

of cognitive impairment and has an etiologically mixed presentation involving a cerebrovascular disease or other types of dementia. As with pre-clinical AD and MCI, biomarkers such as low CSF $A\beta_{142}$; positive PET amyloid imaging; elevated CSF tau; and disproportionate atrophy of medial, basal, and lateral temporal lobes, and medial parietal cortex observed through MRI imaging could provide further support for the diagnosis of dementia due to AD pathology; however, their use for diagnostic purposes is not yet advocated (McKhann et al. 2011). Although FDG-PET ([^{18}F] fluorodeoxyglucose positron emission tomography) is already used in clinical practice to differentiate AD from other types of dementia, preventing the prescription of inappropriate medications for those with frontotemporal dementia or dementia with Lewy Bodies, the hasty and inappropriate use of amyloid imaging for AD diagnosis is cautioned against. A negative result on an amyloid PET scan indicates reduced likelihood of AD as the underlying cause of cognitive impairment; however, a positive result does not establish differential diagnosis between AD and other amyloid-beta disorders such as dementia with Lewy bodies or cerebral amyloid angiopathy (Marcus, Mena & Subramaniam 2014). Furthermore, a positive result may be incidental since cognitively-normal adults could also exhibit age-related increase in cerebral amyloid (Atri 2016). As such, when using amyloid PET imaging to aid in AD diagnosis, it is important that other clinical information are considered, standardized protocols are followed, and the procedure and scan interpretation are performed by staff and clinicians with expertise in neurodegenerative disorders (Marcus, Mena & Subramaniam 2014). Though cognitive and behavioural tests and in the future, biomarkers can be used in diagnosing dementia or cognitive impairment due to AD pathology, neuropathologic examination to determine Aβ deposition, abnormal tau accumulation, and neuritic plaques (Hyman et al. 2012) is still the

definite method for determining whether an individual's cognitive impairments are due to underlying AD pathology.

III. Pathophysiology of Alzheimer's Disease

Considering that Aβ deposition, abnormal tau accumulation, and neuritic plaques (Hyman et al. 2012) mainly characterize AD pathology, progression of the disease can be relatively related to pathophysiological changes associated with these biological hallmarks. In addition, a number of these pathophysiological changes can be used as biomarkers for early detection and confirmation of AD diagnosis (Niemantsverdriet et al. 2017). Although there are ethical issues that arise from the development and clinical application of biomarkers, a number of which are extensively discussed elsewhere (Porteri et al. 2017; Vanderschaeghe, Dierickx & Vandenberghe 2018), their relevance to this thesis is in their use in DBS clinical trials for AD. As will be discussed in Chapters 4 and 5, the use of biomarkers would ensure that DBS trials for AD really include individuals who have pathophysiological hallmarks associated with the disease. Under the principles of non-maleficence and justice (Beauchamp & Childress 2013), including people who do not have AD-associated pathologies in trials involving technologies that target AD-associated neurobiological changes and are highly invasive in nature could expose individuals that have a lesser prospect of benefit to a great amount of risk and unnecessary harms.

Prior to the clinical diagnosis of AD, AD pathology could have started to occur ten or more years before. It is postulated that AD starts with a long asymptomatic phase wherein AD-associated pathological processes progress, and biomarkers of these processes could

indicate risk of progression to MCI and even to dementia. AD pathology is proposed to begin with Aβ peptide accumulation either through abnormal processing or clearance; however, other factors such as cytoskeletal, inflammatory, metabolic, mitochondrial, synaptic, neuronal, and other age-related changes could also play key roles in AD pathology onset. Following these initial processes, synaptic depletion, accumulation of intracellular hyperphosphorylated tau forms, neuronal loss and atrophy, glial activation, and neural dysfunction could then follow (Sperling et al. 2011). Deposition of Aβ dimers, trimers, and oligomers may act intracellularly and extracellularly and engage both lipids and proteins, causing changes in the distribution or activity of neurotransmitter receptors and associated signalling molecules, disruption of intracellular calcium homeostasis, and impairments of axonal transport and mitochondrial functions (Huang & Mucke 2012). Aβ deposition starts as small groups of diffuse plaques in the neocortex then spreads through allocortical regions and eventually to diencephalic nuclei, the striatum, and cholinergic nuclei of the basal forebrain. After which, it further spreads to several brain stem nuclei and lastly to cerebellar regions (Thal et al. 2002).

Another hallmark of AD is the formation of neurofibrillary tangles, made up of hyperphosphorylated and acetylated tau that causes the inhibition and disassembly of microtubules, which then leads to interference of neurotransmission (Huang & Mucke 2012; Raskin et al. 2015). Spread of neurofibrillary tangles starts at projection cells in the transentorhinal region, then extends into the entorhinal region proper, and eventually proceeds into both the hippocampus and the temporal proneocortex. After which, they further spread into the association areas of the adjoining neocortex proceeding

superolaterally and finally extending into the primary areas of the neocortex (Braak & Braak 1997).

Taken together, the deposition of Aβ plaques, neurofibrillary tangles, and the neuronal and glial reactions to them result to loss of neurons in regions such as the entorhinal cortex and hippocampus and loss of neuronal processes (Huang & Mucke 2012). Loss of neurons and thus regional atrophy usually start years before dementia onset and in projection neurons of the medial temporal lobe (MTL), resulting to early memory deficits. Following damage to MTL-originating inputs, neocortical regions receiving inputs from the MTL exhibit reduced activity and decreased metabolism and blood flow. Eventually, these lead to the disintegration of axons connecting these neocortical regions to other cortical regions, potentially resulting to atrophy of the corpus callosum (Smith 2002). Overall, the atrophy observed in the MTL, cortex, and in the corpus callosum results to an aberrant network activity in the brain that interferes with intricate processes underlying memory, learning, and other cognitive functions (Huang & Mucke 2012). Such aberrant network activity is well reflected by electrophysiological changes in brain activity, starting even from pre-clinical stages of the disease. For instance, increased θ activity is associated with impaired cognition during early stages of AD, and as the disease progresses, δ activity increases and α activity decreases. These changes correlate not only with cognitive decline but also with hallucinations, behavioural disturbances, declining functioning, and incontinence. These electrophysiological changes also correspond with metabolic and neuropathologic changes in a number of cortical areas and in the synchronicity between hemispheres (Holston 2015).

IV. Genetics of Alzheimer's Disease

Given that Aβ deposition, abnormal tau accumulation, and neuritic plaques (Hyman et al. 2012) mainly characterize AD pathology, genetic factors associated with their development could give clues on individual predisposition to AD. As explored and elaborated in Chapter 5, the identification of individuals with strong genetic predispositions to AD could be critical in the design of clinical trials. Considering that individuals who possess autosomal-dominant AD-associated mutations could also have an earlier and more aggressive disease course (Rademakers, Cruts & Van Broeckhoven 2003), it is important to identify associated ethical issues that arise from their inclusion and potential modifications that have to be made in the design of clinical trials to ensure that these individuals are not unjustly harmed by trial participation.

Genetic studies have established rare autosomal dominant forms of AD in people with mutations in their *APP*, *PSEN1*, or *PSEN2* genes, which play roles in amyloid beta production, and those with Down syndrome who may have a third copy of the APP gene. People having these mutations may develop AD before they reach 60 and even as young as in their mid-20's (Chouraki & Seshadri 2014; Ringman et al. 2014). People with AD pathology who develop dementia before 65 are referred to as people with early-onset AD (EOAD). Although the 65-year-old cut-off point has no biological significance and is mainly an indicative of social divide in terms of employment and retirement age (Rossor et al. 2010), it has been reported that people with EOAD usually have a more rapid disease progression and also have more pronounced brain pathology compared to those who develop AD symptoms after 65 (Rademakers, Cruts & Van Broeckhoven 2003). In addition, they have a much shorter survival

time; much more prevalent language disturbance (Seltzer & Sherwin 1983); exhibit other atypical symptoms such as visual agnosia, apraxia, dyscalculia and executive dysfunction (van der Flier et al. 2011); have a higher prevalence of additional non-cognitive neurological symptoms (Wu et al. 2012); and exhibit more severe temporoparietal junction atrophy (Frisoni et al. 2005).

At least 62% of people with EOAD have a history of AD in the family (Campion et al. 1999), with mutations in *APP*, *PSEN1*, or *PSEN2* ascribed as the most common cause of early-onset familial AD (EOFAD). The *PSEN1* gene is the most frequently mutated and accounts for most EOAD cases, making up 30 to 70% of familial EOAD (EOFAD); followed by *APP* that accounts for 10 – 15% of EOFAD cases; and lastly, by *PSEN2* that accounts for less than 5% of all EOFAD (Bird 1993; Cacace, Sleegers & Van Broeckhoven 2016). Mutations in *APP* result to its aberrant processing and increased Aβ42 secretion, whereas mutations in *PSEN1* or *PSEN2* lead to aberrant cleavage of APP by γ-secretase, resulting in an overproduction of Aβ42 (Rademakers, Cruts & Van Broeckhoven 2003). Overall, this leads to the biological cascade causing the observed cognitive defects in AD. Interestingly, disease onset and disease progression also differ depending on the mutated gene and the region of mutation. For instance, the age of AD onset in *PSEN1* mutation carriers is between 30 and 50 years old, 40 to 70 years in *PSEN2*, and 45 to 60 years in those having a mutation in *APP*. Moreover, atypical presentations such as language impairment and behavioral symptoms such as delusion, hallucinations, and apathy have been observed in those with *PSEN1* or *PSEN2* mutations (Cacace, Sleegers & Van Broeckhoven 2016). Certain *APP* mutations have also been linked to cases of congophilic angiopathy (Bird 1993), which can lead to leukoencephalopathy, stroke-like episodes, haemorrhage, and cortical calcification (Wu et al. 2012).

Although mutations in these genes have been attributed to AD onset, people having an autosomal dominant mutation in these genes account for only less than 1% of those affected with AD (Schindler & Fagan 2015). Most AD cases occur later in life and are multifactorial. Although these late-onset cases are not due to specific mutations on a single gene, they also have a strong genetic component, albeit more complex and heterogeneous. APOE, which plays a role in the clearance of soluble Aβ and Aβ aggregations, has been associated with late-onset AD, particularly in people with a copy of the *APOE* ε4 allele, which is believed to be less effective in Aβ clearance. Having an *APOE* ε4 allele could also reduce the age of onset of AD by roughly 10 years (van der Flier et al. 2011), and even make its onset earlier for people who have AD-associated mutations in *APP*, *PSEN1*, or *PSEN2* (Bird 1993; Wijsman et al. 2005).

Genome-wide association studies (GWAS) together with functional variant and pathway identification have also been utilized to identify other genes involved in AD. Although none of the risk loci were found to have an effect on AD risk similar in extent to that of APOE ε4, several promising genes have been identified including *Clusterin* (CLU), *Sortilin-related receptor 1* (*SORL1*), *ATP-binding cassette subfamily A member 7* (*ABCA7*), Bridging integrator 1 (*BIN1*), *Complement component (3b/4b) receptor* (*CR1*), *CD33* (Van Cauwenberghe, Van Broeckhoven & Sleegers 2015), *PICALM*, *BIN1*, *MS4A*, *EPHA1*, *CD2AP*, and *ABCA7* (Chouraki & Seshadri 2014). In addition to identifying genetic mutations associated with AD, current studies are also starting to explore gene expression changes, gene-environment interactions, and epigenomic modifications including DNA methylation and hydroxymethylation and microRNA deregulation (Chouraki & Seshadri 2014; Song et al. 2015). Ultimately, elucidating the genetic and epigenetic underpinnings of AD would provide insights

on its diagnosis and would also help predict response to different forms of treatment (Ringman et al. 2014).

V. Pharmacologic Management of Alzheimer's Disease

Although AD was first reported over 110 years ago (Dahm 2006), there are still no approved disease-modifying treatments available. Currently, only six drugs have been FDA-approved for the management of AD; however, none of them stops disease progression (Alzheimer's Association 2015) or treats the underlying pathology. Moreover, the benefits of these drugs extend only for an average of six to 24 months (Broadstock, Ballard & Corbett 2014). With the failure of several drug trials (Cummings, Morstorf & Zhong 2014; Amanatkar, Papagiannopoulos & Grossberg 2017) and the retreat of big pharmaceutical companies from dementia research (Rinaldi 2018), only a few approved substances are available to address the cognitive dysfunction of people with AD. This underscores an ethical need for governments and other institutions to review their strategies and funding towards dementia research, particularly in the development and translation of new drugs (Rinaldi 2018) and other forms of therapy.

Given that early loss of basal forebrain cholinergic neurons occur in AD (Mangialasche et al. 2010), four of the approved drugs (tacrine, donepezil, rivastigmine, and galantamine) are acetylcholinesterase inhibitors, which act through enhancing cholinergic neurotransmission by decreasing acetylcholine breakdown (Anand, Gill & Mahdi 2014), and are mainly prescribed for mild to moderate AD (Broadstock, Ballard & Corbett 2014) with the exception of donepezil, which is prescribed for all AD stages in the USA (Mangialasche et al.

2010). Donepezil, rivastigmine, and galantamine might also have a potential neuroprotective activity by influencing APP processing and decreasing Aβ production, influencing the expression of AChE isoforms, and increasing the expression of nicotinic receptors (Nordberg 2006). Monotherapy with these drugs has been shown to improve cognitive function, slow the pace of cognitive decline, and reduce behavioural symptoms (Anand, Gill & Mahdi 2014) in people with mild to moderate AD (Tsoi et al. 2019).

The other FDA-approved drug, memantine, is an uncompetitive NMDA antagonist that blocks persistent and pathologic NMDA activation in AD and is prescribed for moderate to severe AD (Anand, Gill & Mahdi 2014). Memantine might also have neuroprotective effects by decreasing Aβ toxicity, preventing tau hyperphosphorylation, decreasing microglia-associated inflammation, and increasing astroglia-released neurotrophic factors (Mangialasche et al. 2010). The last drug, which has only been approved in 2014 (Alzheimer's Association 2015), is Namzaric™, which is a combination of extended-release memantine and donepezil and is a potentially more convenient once-daily regimen for patients with moderate to severe AD (Greig 2015).

VI. Therapeutic Modalities Being Investigated for AD

Since there are currently no approved disease-modifying or -stopping therapies for AD, there is a pressing ethical need to explore several treatment modalities to reduce the health and economic burden brought by AD to affected individuals and to society. Drugs and biologics that target amyloid beta and hyperphosphorylated tau production and accumulation; modulate neurotransmitter release; target mitochondrial dysfunction and

oxidative stress; counter inflammation; lower cholesterol; provide neuroprotection; encourage neurogenesis; inhibit apoptosis; modulate nitric oxide synthase; and alter epigenetic changes such as DNA methylation, histone acetylation, and noncoding RNA production are currently being tested, with several already undergoing clinical trials (Adwan & Zawia 2013; Kumar, Singh & Ekavali 2015). Moreover, other non-drug approaches such as cognitive rehabilitation, cognitive training, cognitive stimulation therapy, and physical exercise are being actively investigated for improving cognition in people with MCI and/ or dementia (Corbett & Ballard 2012). The potential of cell-based therapies by transplantation of autologous progenitor cells or neurons derived from cell reprogramming for neuroprotection or neuronal and glial replacement is also being explored (Felsenstein et al. 2014; Kazmerova et al. 2013). In vivo viral- or liposome-mediated delivery of genes to promote growth factor expression or to facilitate siRNA-mediated knockdown of proteins involved in the amyloid beta pathway are also being done in animal models and in a few clinical trials (Nilsson et al. 2010). Lastly, given the aberrant network function in AD, neuromodulation with non-invasive techniques such as transcranial magnetic stimulation (TMS) (Cantone et al. 2014) and transcranial direct current stimulation (tDCS) (Cotelli et al. 2014; Hsu et al. 2015) and with invasive methods such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS) (Laxton, Stone & Lozano 2014) are being explored as well.

Although the focus of this thesis is on invasive treatment modalities that primarily aim to improve the cognition of people with AD, it is important not to discount the importance of social and environmental interventions that provide additional support and help improve the quality of life and well-being of people with AD and their caregivers (Quinn et al. 2016; Vandepitte et al. 2016; Whitlatch & Orsulic-Jeras 2018). In addition, evaluating the value of

interventions, regardless of their nature and invasiveness, should always take into account effects that extend beyond the biology of the person with AD, acknowledging how they could also influence daily function and living, relationality, and sociocultural integration.

In this dissertation, Chapters 4 and 5 discuss the ethical issues associated with clinical trials of DBS for people with AD. These chapters critically examine the scientific validity, recruitment criteria, informed consent procedure, study design, measured outcomes, and communication of results of these trials using the four key principles of bioethics (Beauchamp & Childress 2013) and literature on ethical issues on clinical trials involving people with AD and on the use of DBS for Parkinson's disease and the extension of its application to other conditions. This framework, which utilises an applied and pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) to evaluate different clinical trial aspects, can then be extended to evaluate ethical issues arising from other biotechnological interventions such as cell implantation and gene therapy, as demonstrated in publications incorporated in Chapter 7.

Part II: Beyond Neurobiology: Alzheimer's Disease and Selfhood

Alzheimer's disease significantly impacts both semantic and episodic memory, not only affecting verbal fluency and naming but also causing loss of memories (Gold & Budson 2008; Jahn 2013), especially those that occurred before or shortly after disease onset (Sagar et al. 1988). Episodic memory deficits could lead to loss of autobiographical information containing memories for specific personal experiences at a particular time and place (El Haj et al. 2015). These autobiographical memories contribute to self-narratives and self-

knowledge, allowing integration of past and present selves that enables a sense of identity continuity (Addis & Tippett 2004) and a coherent sense of self. As such, AD could threaten a person's sense of self when a person with AD is unable to reconcile past experiences that he or she still remembers with her most recent experiences. This in turn could result to a petrified and outdated sense of self in which people with AD mainly have the identity of their former selves prior to dementia (Mograbi, Brown & Morris 2009). In addition, the inability of people with AD to reliably retrieve skills and memories constituent of their categorical self could impair the continuous creation of self-narratives, memories, and a self-defining identity (Ronch 1996). Awareness of memory and cognitive deficits, which could also lead to reduced social interaction, ultimately causes distress not just to the person with AD but also to caregivers (Maki et al. 2012).

The concept of selfhood is important in determining ethical issues associated with DBS trials for AD as the potential loss of a person's sense of self has profound implications on his or her ability to provide consent and on how he/she perceives intended and side effects of an intervention (Viaña & Gilbert 2018). How AD could affect a person's sense of self, and the ethical issues associated with these effects on his or her capacity to consent to an invasive neurotechnological trial and ability to make eventual trial-related decisions, are explored in Chapter 6. The main purpose of this section is to provide readers a more extensive introduction and overview of the literature on effects of AD on the self that are presented in the paper comprising Chapter 6 (Viaña & Gilbert 2018). As this is a mainly descriptive section, no ethical arguments are forwarded in this section. These arguments, which incorporate findings from empirical studies that are reviewed in this section, are presented in Chapter 6.

Several qualitative and quantitative studies have been performed to determine the effect of AD on a person's sense of self. Different studies have used a range of models of the self to investigate how AD affects people's selfhood and identity. These models include the social constructionist theory, an interactionist perspective, embodied selfhood, self as a narrative, autobiographical memory in selfhood, role identity, self-recognition, and self-knowledge (Caddell & Clare 2010).

The framework that has been most widely used in studies is the social constructionist model, which states the importance of language in the creation of a social reality that is a product of cooperative and active enterprise of people in relationships (Gergen 1985; Caddell & Clare 2010). Applying this model in selfhood studies, three aspects of the self can be derived and investigated through interactions of people with AD with other individuals or with the interviewer. Self 1 is the experience of singularity or psychological continuity over time and can be determined by a person's use of personal pronouns such as "I", "me", "my", and "mine" and/or gestures such as pointing to one's self that index a person's unique and singular position in time and space. Self 2 refers to the self in terms of past and present physical and psychological attributes, beliefs, and judgment of these attributes. Self 3 consists of the persona that an individual displays socially, along with the attributes associated with that particular role, as a result of co-creation with one or more individuals (Harré 1991; Sabat & Harré 1992; Sabat & Collins 1999).

An illustration of how these three aspects of selfhood are investigated in a person with AD is in the case study performed by Sabat and Collins (1999) on a 63-year-old woman with probable AD (Mrs. F). In her responses to interview questions, Mrs. F still demonstrated an

intact Self 1 through regular use of first-person pronouns that indicated her opinions as being hers. Her Self 2 was also relatively preserved as she clearly took pride in past attributes such as her musical background, education, and talents; and of her sense of independence. Mrs. F was also cognizant of new attributes she has acquired due to AD, which include "memory and linguistic problems, problems organizing sequences of movement, and difficulty taking care of aspects of family life that had been her domain in earlier, healthier days" (p. 16, Sabat & Collins 1999). She also demonstrated awareness of differences in her past and present abilities and expressed frustration on her disease-related attributes. With regards to her Self 3, she presented herself as a teacher with a degree in music rather than as an AD sufferer. Sabat and Collins (1999) noted that Mrs. F preferred to be seen as someone with positive attributes through her past profession as a teacher rather than as someone with AD in an adult day care program.

The study of Sabat and Collins (1999) demonstrated that several aspects of the three senses of self could remain intact in a person with AD. This has also been the observation in most other studies that investigated selfhood using Harre's social constructionist theory (Caddell & Clare 2010). For instance, a later study done by Sabat (2002) involving a different woman with probable AD demonstrated all three aspects of the self to still be mostly intact. The woman still used first person pronouns, indicative of an intact Self 1. She also was able to refer to her previous ability to find the exact words for her thoughts, being a former academic, and shared her frustrations from not being able to use the most appropriate words as a result of AD (Self 2). In connection with her acknowledgement of linguistic difficulties, her expression of her Self 3 as a former academic and social worker has been limited. Although Dr. M's training as an academic and social worker could enable her to identify organizational

problems in the support group she was attending, she was hesitant to point them out due to fear of embarrassment from her difficulties in finding the correct words. After Sabat (2002) engaged and positioned her as an insightful person, seeing her as someone with two advanced degrees rather than as an AD patient, she enjoyed subsequent conversations discussing how the support group sessions went, allowing her to express her social persona as a social worker. Sabat (2002) noted that the initial hesitation of Dr. M to express herself as an academic and a social worker can indicate a potential loss of Self 3; however, this was not due to the pathology itself but rather could be a result of the attitudes of healthy others to limit the social persona of a person with AD to that of a 'burdensome, dysfunctional patient' by focusing on his or her diminished attributes due to the disease. Given that Sabat (2002) encouraged Dr. M to share her insights, such loss of Self 3 was averted, allowing Dr. M to express her former social persona as an academic, colleague, and mentor in subsequent interviews.

Although Self 1, Self 2, and Self 3 were not really lost in Dr. M and Mrs. F in the studies of Sabat (2002) and Sabat and Collins (1999), respectively, other studies have pointed out to a possible loss of different aspects of the Self. For instance, Small et al. (1998) have demonstrated a possible deterioration in or loss of Self 1 based on the reduced capacity or inability to refer to one's self in conversations. They reported that more than half of people with dementia in their study, in a sample with mostly people with AD, did not use first pronouns when interacting with other people. However, they noted that these people were still able to defend their rights in conflicts and call staff by their names, which Small et al. (1998) interpreted as demonstrations of the integrity of the self via non-verbal behaviours and manners of addressing people. Fazio and Mitchell (2009) also reported a decrease in the

usage of personal pronouns with increasing cognitive impairment; however, calculations on the rate of pronoun and attribute word usage indicated similar rates of usage among those with no, mild, and moderate cognitive impairment. This suggests that decreased personal pronoun use is mainly a result of cognitive and linguistic production deficits, but not of inability to refer to one's self. With regards to a possible loss of Self 2, there were reports of a person with AD mixing past and present events, and several individuals who did not recognize or even markedly deny their memory deficits (Sevush & Leve 1993; Skaalvik et al. 2016). Finally, as already suggested by Sabat (2002) in the case of Dr. M., the expression of certain Selves 3 or social selves by people with AD might be limited due to healthy others constraining the social persona of a person with AD to that of a 'burdensome, dysfunctional patient (Sabat 2002; Sabat 2003) and to malignant positioning of healthy behaviours as dysfunctional and certainly due to the diagnosis (Sabat & Harré 1992; Sabat & Collins 1999; Sabat, Napolitano & Fath 2004; Sabat 2005; Sabat & Gladstone 2010).

Since Harre's social constructionist theory will act as the base of an extended tripartite model of the self that will be used in exploring how DBS for AD could impact selfhood in Chapter 6, the remaining models used in other qualitative and quantitative studies will only be briefly described. Another commonly used framework in qualitative studies is the interactionist perspective, which posits that the self is based on social constructs that are rooted in interactions with other people through conversations and non-verbal behaviour (Caddell & Clare 2010). An interesting study that used this approach is that of Fontana and Smith (1989) where people with AD in a senior day-care centre were observed for a year, taking note of their daily activities and interactions with staff and other people with AD. Fontana and Smith (1989) noted that in certain people with AD, the self is deteriorated to a

point that only internalized social norms and customs, basic emotional needs such as love and affection, and manifestations of selfishness and egocentrism remain in the patient. They have mentioned instances when people with AD would answer the phone when it rang but then would not be able to identify what they are holding; conversations between people with AD where one is just singing nursery rhymes while the other person is mumbling nonsense; and interactions where people with AD express emotions suggesting of engagement in a dialogue, only to eventually utter non-sensical statements (Fontana & Smith 1989).

Other qualitative studies employed the concept of embodied selfhood, which sees the self as reflected in bodily actions such as appearance, social etiquette, response to music, caring, politeness, and culture- and class-specific gestural communication and behaviour (Kontos 2004, 2005). Using such framework of selfhood still suggested that people with AD have manifestations of selfhood through maintenance of their appearance, awareness of their surroundings, interaction with other people, and construction of an autobiographical memory-based narrative, albeit to varying degrees. For instance, by observing residents suffering from dementia in an Orthodox Jewish long-term care facility, Kontos (2004) found that people with AD still manage to maintain their appearance by applying lipstick or wiping food on face with a bib; exercise social etiquette by expressing gratitude or covering one's mouth when yawning; show care for others by comforting them when they show signs of distress; dance when Yiddish songs are being played spontaneously in the hallway; and use gestures such as gazing to express interest or disinterest in communicating with other residents. In addition to evaluating selfhood based on corporeal awareness through social interaction, bodily action, and spatial navigation (Kontos 2004), other qualitative studies investigated the ability of participants to share personal narratives. Although people with AD

could still manage to access and share personal accounts of their life and use them to maintain a self-schema (Usita, Hyman Jr & Herman 1998), such narratives could be compromised either through chronological fragmentation or omission, and they might not be as cohesive and comprehensive as of those who do not have AD (Caddell & Clare 2010).

Quantitative approaches have also been utilized, using scales to evaluate strength and valence of identity in people with AD; role identities from the person's and family members' perspectives; self-recognition using mirrors, photographs, and videotapes; and knowledge of one's name, job, and personality traits, which are compared with ratings from family members. Overall, results from these quantitative studies show people with AD to have a vaguer and weaker sense of identity; to forget or place less significance in role identities, especially occupational roles; to less likely be able to recognize themselves in the mirror, videotapes, and recent photographs; and potentially, to less accurately rate present attributes and personality traits, especially for those with severe AD (Caddell & Clare 2010).

Overall, results from quantitative and qualitative psychological and sociological studies on people with AD suggest that although selfhood is not completely lost in these individuals, several aspects of it can be affected by the disease, with varying severities depending on disease stage and on interaction with other people. Of special note is how the framework used in a number of these studies can be utilised to investigate how a particular intervention could further affect the selfhood of someone with Alzheimer's disease. Considering that Sabat and Harre's tripartite model of selfhood has been one of the most commonly-used qualitative frames, this model could be extended for use in the reflection of possible changes in the selfhood of people with AD, due to the AD pathology and its cognitive

effects and also due to both the intended and unintended effects of a particular intervention such as DBS. Chapter 6 (Viaña and Gilbert 2018) builds on Sabat and Harre's tripartite model of selfhood, incorporating frameworks from other qualitative and quantitative studies on the effect of AD on selfhood and discussions on the plausible effects of DBS on the selfhood and identity of individuals receiving this therapy, to explore possible DBS-associated changes in the self of people with AD and the ethical concerns that could arise from them.

Chapter Three. Deep Brain Stimulation: Effects on the Brain and Implications on the Self

The first six sections of Chapter 3 review the history, medical procedure, modes of action, and risks and possible side effects of deep brain stimulation, which will be useful in understanding scientific, medical, and ethical points raised in Chapters 4 (Viaña et al. 2017), 5 (Viaña, Bittlinger & Gilbert 2017), and 6 (Viaña & Gilbert 2018). The last section (Section VII) provides a descriptive overview of philosophical reflections on the possible effects of DBS on selfhood and identity. This information would help readers better follow the arguments forwarded in Chapter 6 (Viaña & Gilbert 2018), which hypothesises possible effects of DBS on the selfhood of people with AD and their ethical implications for the informed consent procedure and the design of DBS for AD clinical trials. This chapter also includes three publications that I co-authored. These publications report on feelings of self-estrangement of people with Parkinson's disease post-DBS (Gilbert et al. 2017); reflect on the lived experience of someone with PD who experiences unintended psychiatric sequelae (Gilbert & Viaña 2018); and caution against hype in neuroethical discussions on the effects of DBS on personality, identity, agency, authenticity, autonomy, and self (Gilbert, Viaña & Ineichen 2018).

I. History of and Recent Progress on DBS

From 46 A.D. until the 1700's, electricity had been used for treating disorders such as headaches, epilepsy, haemorrhoids, and gout (Gionfriddo et al. 2013). One of the very early demonstrations was made by the first-century Roman physician Scribonius Largus wherein an electric ray (*Torpedo torpedo*) is placed on the spot which is in pain (Wu 1984). However, it was only in 1802 when electrical stimulation of the brain was shown to stimulate facial

muscular contraction in cadavers and only in 1874 when experiments on a patient showed that electrical stimulations of the brain result to a variety of muscular contractions and eventually seizures (Gionfriddo et al. 2013). The first therapeutic application of instrument-induced electrical stimulation of the brain was reported in 1936 and in 1937 when it was used to localize the firing point for epilepsy (Penfield 1936) and in mapping cortical somatic motor and sensory representation (Penfield, Wilder & Boldrey 1937), respectively. On the other hand, the use of chronic electrical stimulation of subcortical targets as therapy was first performed in the 1950s to treat psychiatric illness and pain and for behavioural modification, and subsequently for epilepsy and movement disorders such as Parkinson's disease (Hariz, Blomstedt & Zrinzo 2010; Hariz 2012). Although DBS for psychiatric and neurologic disorders was first performed in the 1950s, the modern DBS that is employed now was heralded in 1987 when high frequency stimulation (HFS) of the thalamic nucleus ventralis intermedius was systematically tested on patients with drug-resistant bilateral extrapyramidal tremor (Benabid et al. 1987).

Since the first systematic test of modern DBS on patients with tremor (Benabid et al. 1987), DBS has received regulatory approval for a number of conditions. In the USA, it has received pre-marketing approval from the FDA for unilateral thalamic stimulation for tremor in the upper extremity for patients with essential and Parkinsonian tremor in 1997 (Alpert 1997), and for bilateral stimulation of the internal globus pallidus (GPi) or subthalamic nucleus (STN) for advanced, levodopa-responsive Parkinson's disease in 2002 (Schultz 2002). Moreover, it has received a Humanitarian Device Exemption from the FDA for unilateral or bilateral stimulation of the GPi or STN to aid in the management of chronic, drug-refractory dystonia in 2003 (Schultz 2003), and for bilateral stimulation of the anterior limb of the

internal capsule (AIC) for chronic, severe, treatment-resistant obsessive-compulsive disorder (OCD) in 2009 (Tillman 2009). In Europe, various DBS manufacturers have also received Conformité Européenne (CE) marks for the treatment of various disorders such as essential tremor, symptoms of Parkinson's disease, dystonia, OCD, and epilepsy (Sarem-Aslani & Mullett 2011).

As of 2017, more than 150,000 people worldwide have received Medtronic-manufactured DBS implants for the treatment of movement disorders (Medtronic 2018). Currently, DBS is tested for a wide range of conditions including headache disorders (Altinay, Estemalik & Malone 2015); psychiatric conditions such as depression, anorexia nervosa, addiction and substance abuse disorder, aggressive behaviour, and post-traumatic stress disorder (Cleary et al. 2015); and dementia-causing disorders such as Alzheimer's disease (Hescham et al. 2013). In addition, registered trials on movement disorders are continuously being performed to provide further evidence for efficacy, determine the benefit of early surgery, identify novel brain targets (Kalia, Sankar & Lozano 2013), and determine other movement disorders such as Huntington's disease, Tourette syndrome, and ataxia in tremor patients (Fasano & Lozano 2015) where DBS could be applicable. The expansion of the populations for which DBS is offered to and the testing of DBS for other neurologic and psychiatric indications raise a wide range of ethical concerns, which have been explored and raised in numerous bioethical discourses. These concerns range from the assessment of decisional capacity and therapeutic misconception of prospective participants (Fisher et al. 2012) to the proper selection of potential recipients and the design of clinical trials (Grant et al. 2014). In addition to concerns that directly address aspects of the trial, there have also been discussions on the implications of both intended and side effects of DBS on the selfhood,

agency, and personal identity of people with neurologic or psychiatric disorders (Mathews 2011; Nyholm & O'Neill 2016). This thesis focuses on the ethics of DBS in people with AD, with Chapters 4 (Viaña et al. 2017) and 5 (Viaña, Bittlinger, & Gilbert 2017) directly addressing the ethical issues raised by the design and conduct of the clinical trials and Chapter 6 (Viaña & Gilbert 2018) broadening the discussion to how DBS could potentially impact the selfhood of people with AD and the accompanying implications of these possible effects on consent for participation and care provided throughout a clinical trial.

II. Deep Brain Stimulation Surgery

In a typical DBS procedure, initial targeting of the brain region of interest, which is guided by neuroimaging that is then co-registered with stereotactic frame-based markers, is performed prior to surgery (De Jesus et al. 2015). During surgery, microelectrode recording is used to verify trajectory to the target and confirm targeting of the desired region. Upon confirmation, the microelectrode is withdrawn, and one or more quadripolar leads, which currently have band-shaped structures 1.5 mm long and spaced either 0.5 mm or 1.5 mm apart, are implanted in the target structure and secured to the skull. The leads will then be connected to an externally programmable implanted pulse generator (IPG), which will deliver continuous electrical stimulation (Okun 2012; Gionfriddo et al. 2013; De Jesus et al. 2015). Constant voltage stimulation is provided in a monopolar or bipolar configuration, which activates a spherical volume of tissue surrounding the lead. Post-implantation and once the patient has recovered from surgery, DBS stimulation parameters can be programmed by clinicians to determine the optimal settings for each patient to maximize relief from disease symptoms while minimizing unwanted stimulation-induced side effects. The voltage,

frequency, and pulse width in specified electrodes can be programmed in current DBS devices, and the stimulation is generally delivered in a regular pattern (De Jesus et al. 2015). As soon as optimal stimulation parameters are set, stimulation is continuous; however, the stimulation parameters can be adjusted as needed and the device might be turned off overnight to preserve battery life (Fitzgerald & Segrave 2015). Overall, total hospital charges for a DBS surgery costs $62,077 for FDA-approved indications and $88,173 for Humanitarian Device Exemptions (HDE) and other emerging indications (Youngerman et al. 2016). The invasiveness and complexity of DBS raise several issues on the acceptable risk-benefit ratio and scientific validity of clinical trials for novel indications, which are further elaborated using the case of DBS for AD in Chapters 4 (Viaña et al. 2017) and 5 (Viaña, Bittlinger, & Gilbert 2017). Furthermore, the high cost of the procedure and the requirement for a multi-disciplinary team imply access issues for certain populations and implementation difficulties in resource-limited settings, issues that are also touched upon in Chapter 4 (Viaña et al. 2017).

III. Possible Modes of Action of DBS

There are a number of mechanisms by which DBS could exert its therapeutic action on symptoms of movement and psychiatric disorders (Figure 2). At the synaptic level, high frequency stimulation (HFS) from DBS is hypothesized to primarily activate axons resulting to antidromic spikes that collide with naturally-occurring movement-related spikes and orthodromic spikes that will propagate to synaptic terminations resulting to either excitatory postsynaptic potentials (EPSPs) or inhibitory postsynaptic potentials (iPSPs), which would then affect the activity of target neurons and nuclei (Hammond et al. 2008; Cheney, Griffin & Van Acker 2013). In addition, neuronal activity changes resulting from HFS DBS could lead to

increased extracellular potassium and inactivation of sodium currents, which may hinder action potential development through a periodic depolarization block, or to an eventual leakage of glutamate from terminals resulting to excitation of postsynaptic elements (Zheng et al. 2011; Florence et al. 2015; Herrington, Cheng & Eskandar 2016). The observed antidromic and orthodromic spikes from DBS, together with the changes in extracellular potassium and the physiologic changes that follow, could then regularize cell firing or generate a new regular activity locked to the stimulation and overall result to an interruption of pathological oscillatory rhythms while preserving the transmission of cortical information (Hammond et al. 2008; Florence et al. 2015).

At a systems and network level, axonal activation brought about by DBS could lead to numerous widespread and heterogeneous effects. These include changes in neurotransmitter release and neuronal excitability in structures directly and indirectly connected to the stimulation nucleus; modification of a network's oscillatory properties and introduction of a regular activity in several nodal points of a network, which ultimately prevents the generation and propagation of pathological synchronized oscillations (Hammond et al. 2008; Deniau et al. 2010); creation of an informational lesion through the stimulated nucleus preventing the transmission of pathological neural signals (Herrington, Cheng & Eskandar 2016); and activation of *en passant* fibres and afferent terminals that could influence activity not only in subcortical structures but of the cortex as well, breaking the phase relationship among neurons and releasing it from a pathological rhythm (Li et al. 2014).

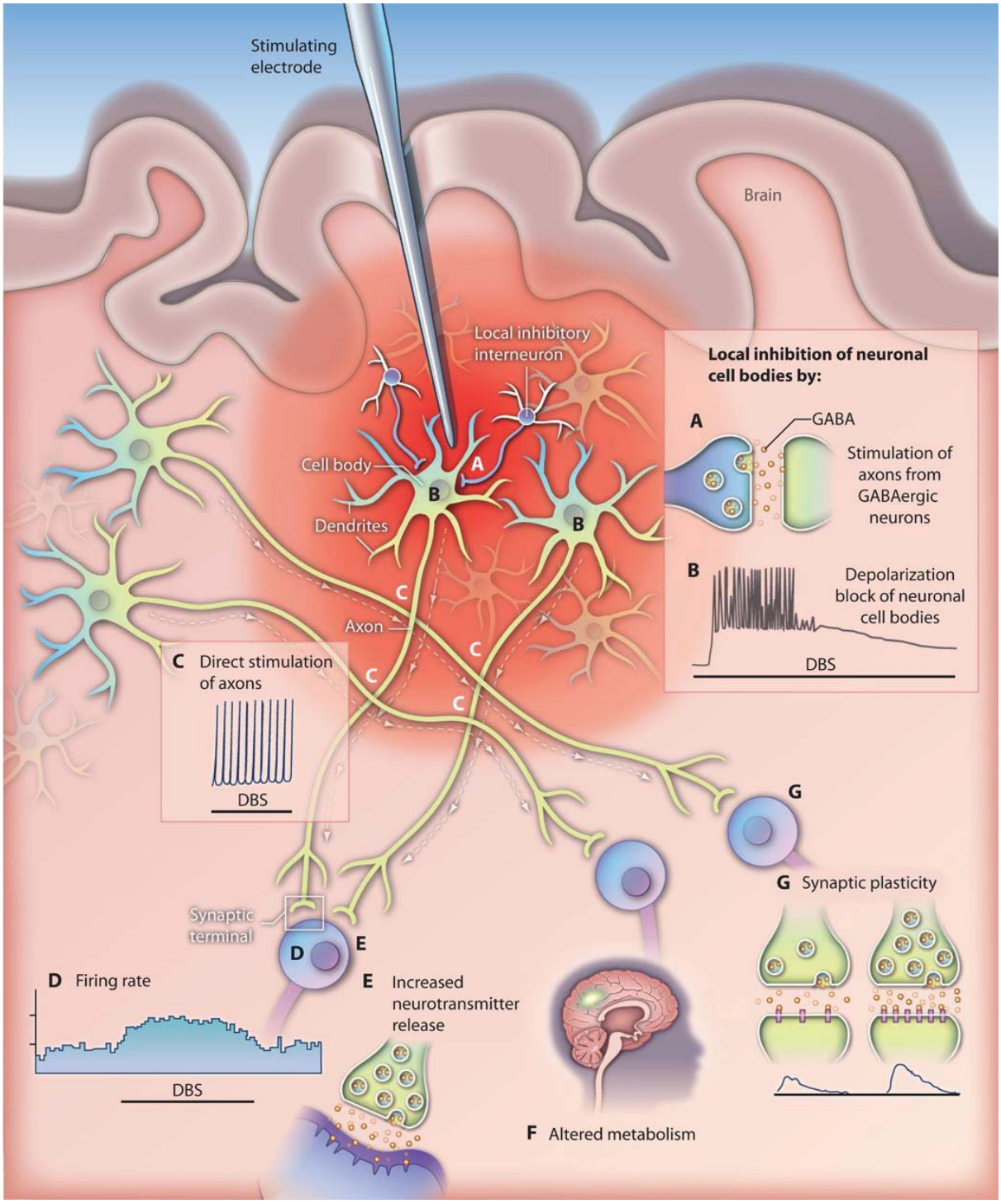

Figure 2. Mechanisms of action of high frequency deep brain stimulation. Inactivation of the target brain region results from (A) release of the inhibitory neurotransmitter GABA and (B) a depolarization block that decreases activity in neuronal soma. In addition, DBS could also lead to (C) stimulation of axons resulting in a tonic, artificial pattern of action potential firing and (D) changes in the firing pattern and firing rate in neurons of connected brain structures, which can be associated with (E) release of neurotransmitters, (F) altered metabolism, and (G) long-term potentiation (figure from Hamani & Temel 2012; © 2012, AAAS).

The described therapeutic effects of DBS based on its physiologic actions at the synaptic and network levels is well illustrated by the effect of subthalamic nucleus (STN) stimulation on Parkinsonian symptoms. During HFS of the STN, pathological activity that gives rise to motor symptoms are suppressed (Rosenbaum et al. 2014) and are potentially replaced by a new HFS-driven pattern that can influence target structures in the basal ganglia network (Garcia et al. 2005). Particularly, STN HFS possibly activates pallido-nigral neurons via the glutamatergic subthalamo-pallidal projections releasing GABA to the substantia nigra pars reticulata (SNR), leading to its inactivation and eventual relief from akinesia in people with PD. In addition, STN HFS generates inhibitory synaptic effects in external globus pallidus (GPe) neurons via antidromic activation of the pallido-subthalamic axons and a local axon reflex. Moreover, given the massive inputs that the STN receives from the pedunculopontine nucleus, HFS of the STN could also give rise to antidromic spikes that could affect neuronal excitability and processing in regions beyond the first-order connections of the STN such as the thalamus, tectum, and brainstem (Deniau et al. 2010). Aside from subcortical structures, DBS could also affect incoming fibres from the cortex, antidromically targeting it in a retrograde manner and releasing it from a pathological rhythm. These DBS actions could overall then lead to suppression and disruption of local beta band oscillations and LFP-spike coherence in several brain regions, which leads to relief from bradykinesia and rigidity experienced by people with PD (Li et al. 2014; Rosenbaum et al. 2014; Herrington, Cheng & Eskandar 2016). Although these effects might also be applicable to DBS in psychiatric disorders, it has been proposed that targeting the STN in PD disrupts a synchronized circuit thereby creating an informational lesion, whereas targeting structures not part of a synchronized circuit such as the medial hypothalamus could have a stimulatory effect (Murrow 2014). As such, therapeutic effects observed in HFS DBS for psychiatric disorders might have a different underlying mechanism

depending on the target structure, the neural networks involved, and the behavioural or cognitive symptom being addressed.

Although HFS DBS has been mainly proposed to affect neural firing patterns (Okun & Oyama 2013) and regulate network activity, other mechanisms could also potentially contribute to its therapeutic effects. DBS might lead to synaptic plasticity-related changes in the neural network such as short-term potentiation (STP), long-term potentiation (LTP) and long-term depression (LTD). It could also have neuroprotective effects by increasing cell survival through reduction of glutamate excitotoxicity, inducing neuroprotective growth factors such as the brain derived neurotrophic factor (BDNF), increasing neuronal precursor cell proliferation, and inducing hippocampal neurogenesis (Herrington, Cheng & Eskandar 2016). Lastly, electrical stimulation from DBS could also trigger astrocytes, leading to altered cerebral blood flow and release of ATP and glutamate, which are neuromodulators that could regulate neuronal synaptic networks. Aside from stimulation during DBS, insertion of the stimulating electrode itself could trigger ATP and glutamate release in addition to producing hypermorphic reactive astrocytes, which can deplete GABA and hyper-excite regions where they are present (Vedam-Mai et al. 2012). Chapter 4 (Viaña et al. 2017) reviews the results of animal studies and clinical trials of fornix DBS, reflecting on how they can be used to improve participant selection and the study design of ongoing and future clinical trials on DBS for AD.

IV. DBS-Associated Medical Risks and Side Effects

DBS is not a risk-free procedure, and a number of adverse side effects have been observed in- and post- surgery and during stimulation. During operation, several patients

(5.1%) experienced adverse events related to electrode placement such as intracranial haemorrhage, subdural haemorrhage, air embolus, and seizure. In the immediate postoperative period, seizure, spinal fluid leak, mental status change, and pneumonia have been reported in 6.1% of patients. A number of patients (4.9%) could also have hardware-related complications such as hematoma or seroma, lead fracture, skin erosion, and infection. Lastly, stimulation-related adverse events including speech disturbance, ballism, eyelid apraxia, and corticospinal effects have also been reported in some patients (5.7%) (Patel et al. 2015). A number of studies and reviews have also reported other adverse events such as delirium, depression, mania, cognitive decline, psychosis, suicidality, anxiety, disinhibition, hypersexuality, weight gain, and emotional change (Appleby et al. 2007; Pinsker et al. 2013). It is important to emphasize though that adverse effects could vary depending on the targeted brain region and condition being treated. For instance, DBS side events occur more frequently when subthalamic rather than pallidal or ventral intermediate thalamic stimulation is performed (Guehl et al. 2003). Overall, adverse events are relatively infrequent in DBS and neurohistopathological findings likewise support the safety of chronic DBS neuromodulation therapy (DiLorenzo et al. 2014); however, it is important to highlight that certain adverse events such as infection and lead failures are serious complications, and intracranial haemorrhage and suicidal ideation and its execution are life threatening (Appleby et al. 2007).

Given the possible complications and adverse side effects that may arise in patients undergoing DBS, novel stimulation protocols via hardware and software innovations are currently being developed to minimize side effects and maximize derived benefits. These protocols include constant current stimulation; interleaving different stimulation parameters to target different symptoms; ability to vary temporal pattern of stimulation; customized field

shaping and current steering for directional stimulation; and non-continuous, scheduled, or adaptive stimulation (Hariz 2014; De Jesus et al. 2015). In addition, advances in structural imaging with fMRI and connectivity visualization with diffusion tensor imaging (DTI) and tractography aim to improve targeting and discrimination of brain structures of interest (Hariz 2014).

In Chapters 4 to 6, the possibility of these side effects occurring are taken into consideration in the discussion of the risks associated with DBS for AD trial participation, while equally emphasizing that differences in the brain region targeted, pathophysiology of the condition, and pharmacologic management among different conditions could influence the adverse events that would occur as a result of DBS surgery and long-term stimulation. Specifically, these chapters review the protocols of different DBS for AD clinical trials to assess whether they have accounted for the possibility of these adverse events occurring and what strategies have been devised to adequately inform the research participants of these risks and minimise harm should any of the mentioned clinical adverse events arise, in line with the ethical principle of non-maleficence (Beauchamp & Childress 2013).

V. Beyond the Clinical: Potential Effects of DBS on Personality, Selfhood, and Socialization

One of the first studies reporting putative the effects of DBS on behaviour, personality, selfhood, and relationships was that of Houeto et al. (2002). This study analysed 24 Parkinsonian patients who were successfully treated by subthalamic nucleus DBS for the presence of behavioural disorders including adjustment disorders, psychiatric disorders, and personality changes. Overall, although motor disability was improved and levodopa dosage

was decreased in at least 60% of the patients, social adjustment was impaired in more than half of the patients. Interestingly, late disease onset was associated with poor postoperative global social adjustment. Furthermore, amplification or decompensation of previously existing psychiatric disorders, such as depressive episodes, generalized anxiety, and behavioural disorders with drug dependence, that have previously passed unnoticed was observed. In addition, more than half of the patients had episodes of mild to moderate emotional hyperactivity. Finally, personality traits were aggravated in a third of the patients. In particular, there was an increase in irritability, lack of initiative, perseveration, lability/moodiness, lack of persistence, lack of planning, inflexibility, poor judgement, insensitivity, impatience, indecisiveness, apathy, and vulnerability to pressure.

Houeto et al. (2002) also provided extensive case reports on five patients in the study. The first patient reported lack of energy, wanted his wife to stay at home the whole day to look after him, and had mood swings with aggression, irritability, and depression. Sexual behaviour with exhibitionism and gambling were also reported. Upon further investigation, the patient had a period of alcohol misuse and hypomania ten years before PD onset, indicating potential worsening of an affective disorder with addictive behaviour.

The second case report is that of a patient whose marriage deteriorated four months post-stimulation, which eventually led to a divorce. His wife reported behavioural disorders with sexual deviancy, heightened libido, and exhibitionism (Houeto et al. 2002). In addition, "the patient showed an interest in games of chance and travelled to foreign countries where he was suspected of leisure tourism" (p. 702, Houeto et al. 2002). It was hypothesized that DBS-induced improvements in the patient's conditions led to expression of his novelty-

seeking and sexually deviant behaviour, which reached the point of his wife being afraid for children in the neighbourhood (Houeto et al. 2002).

The third case illustrates that of a patient who had "reappearance of a severe anxious-depressive state during the stimulation therapy and the exacerbation of familial conflicts" (p. 702, Houeto et al. 2002). This patient had two episodes of severe depression years prior to surgery. Weeks after DBS implantation, he had conflicts with his daughter, complained of sexual dysfunction, and had difficulties in communicating with his wife. Six months post-implantation, the patient had several episodes of depression with sleep disorders and loss of appetite, interest, and inertia. The fourth patient had mild reduction in verbal fluency after surgery and presented emotional hyperreactivity. Specifically, the patient had difficulty controlling the magnitude and range of his emotions, suggesting that he is being overtaken by feelings that he cannot control (Houeto et al. 2002).

The fifth patient had no history of psychiatric disorders, but developed affective blunting and hyperreactivity post-DBS. Four months post-surgery, he complained of loss of initiative, fatigue, and loss of interest in seeing his friends. He highlighted that "Before stimulation, I wanted to be like everybody else. I fought against my disease. Now, I have lost my motivation, I no longer want to do anything, I miss the period when I was fighting" (p. 702, Houeto et al. 2002). His wife also reported a decrease in libido (Houeto et al. 2002).

Overall, Houeto et al. (2002) divided the observed abnormalities post-DBS into five categories. The first one, social maladjustment, can be attributed to communication problems between patients and their spouses as a result of a sudden change in roles, and by difficulties

in integrating into a new socio-familial environment after being disabled for several years. Second, depression was observed, especially in patients with a history of depression, with one patient developing melancholia with major delusions and feelings of guilt in the context of marked anxiety and eventually committing suicide. Third, there was a high prevalence of anxiety in patients. Fourth, a quarter of the patients experienced emotional hyperreactivity, having disabling difficulties in controlling their emotions. Fifth, two patients who had periods of drug dependence in the past and became addicted to levodopa therapy exhibited behavioural disorders such as sexually deviant behaviours.

Other extensive reports on the effects of DBS on the self are that of Agid et al. (2006) and Schupbach et al. (2006) where 29 people with Parkinson's disease were evaluated and interviewed before and after DBS to determine the effect of the intervention on recipients' psycho-social condition. Interestingly, although there was a general improvement in motor and mental function, there was no significant improvement in the patients' Social Adjustment Scale (SAS) scores (Paykel et al. 1971). In addition, the work and marital relations sub-dimensions of SAS also tended to be worse two years after DBS surgery, with 65% of previously-married patients experiencing a conjugal crisis and 64% of those who were working wanting to stop their professional activity.

Psychological interviews in the studies of Agid et al. (2006) and Schupbach et al. (2006) then revealed potential effects of the neurosurgery on the patient's self, spouse and family, and socio-professional life, which help explained the lack of sufficient improvement in social integration following DBS. On potential effects of the surgery on the "self", some patients experienced strangeness from the absence of motor symptoms; loss of aim in life from no

longer dealing with motor impairments; difficulties in dealing with consequences of the disease on their social and professional lives; loss of vital force; persistence of anticipatory thoughts on potential eventual motor problems; and an impression of a dehumanised and device-dependent body due to the leads in their brain. In terms of marital relations, some patients rejected their spouses due to recovery of their autonomy and feelings of being "cured", leading to spouses experiencing difficulties in giving up their role as a caregiver. On the other hand, some patients might be rejected by their spouses who expect them to return to a normal life post-stimulation. Finally, effects on socio-professional affairs include giving secondary importance to work after stimulation and wanting to be socially recognized for their disease. These observations reflect potential changes in the identity in which patients see themselves after DBS surgery, which could be a result of difficulties in re-integrating into their professional and familial environments (Agid et al. 2006).

In addition to the accounts presented by Houeto et al. (2002), Agid et al. (2006), and Schupbach et al. (2006), there have been other cases reported that demonstrated a significant change in personality post-DBS. Mathews, Bok and Rabins (2009) presented a case of a formerly-shy engineer who became extremely outgoing and gregarious, changed his political affiliation, and became an ardent environmentalist post-DBS. Kraemer (2013) referred to a Dutch patient undergoing DBS treatment who developed a permanent manic state, which led him to have excessive debts, altercations with the police, and eventually, psychiatric hospitalization. Interestingly, when the stimulation was turned off, the patient had an accountable and rational state of mind and was capable of making decisions; however, he was physically disabled and bedridden due to PD (Leentjens et al. 2004). Another patient has also developed manic psychosis following subthalamic nucleus stimulation for PD. The patient

lost normal social inhibitions, tried to kiss and embrace people, fell in love with neurologists, engaged in unrestrained shopping for clothes, and felt her sons were conspiring against her. The patient had little insight into her disorder and exhibited impaired judgement (Herzog et al. 2003). This was also observed in a 60-year old man with DBS for PD who was described by his wife as becoming like a spontaneous and difficult teenager post-surgery, wanting to cross an international border without a passport (Bell et al. 2011). Aside from changes in personality, changes in preferences could also occur. Mantione, Figee and Denys (2014) reported a patient who received DBS for obsessive-compulsive disorder (OCD) who developed a sudden and distinct preference for Johnny Cash songs, along with an increase in confidence.

On the more extreme end of the spectrum of potentially DBS-associated changes in behaviour, Goethals and colleagues (2008) reported a 43-year old male patient suffering from Tourette syndrome who received DBS and developed a dissociative response 12 months postoperatively when the stimulation amplitude was increased. Increasing right thalamic stimulation amplitude from 1.5 to 2.4 V resulted to him "anxiously crouching in a corner, covering his face with his hands. He spoke with a childish high-pitched voice and repeatedly insisted that he was not to blame. Sentences were brief and grammatically incorrect. If approached by one of us, he fiercely kicked his feet because he feared being thrown in the basement" (p. 545, Goethals et al. 2008). Interestingly, when the stimulation amplitude was lowered again, the patient returned to normal behaviour but "could not tell what had happened and reported to have been overwhelmed by bad childhood memories" (p. 545, Goethals et al. 2008).

In evaluating the risks associated with clinical trials of DBS for a novel neurologic or psychiatric indication, it is important to consider the possible effects of DBS on behaviour, personality, relationships, and societal integration, in addition to its effect on the brain and on symptoms of the condition in which it is being tested for. Accounts from case studies and systematic empirical investigations that are enumerated in this section are used in Chapter 6 (Viaña & Gilbert 2018) to hypothesise on the possible impact of fornix or NBM DBS on people with AD as a result of both intended and side effects of the intervention. It is essential to consider how these effects could influence a participant's sense of self. This information can then be used to improve the way consent is obtained and the manner in which participants are treated all throughout the trial, in line with the ethical principles of respect for autonomy, beneficence, and non-maleficence (Beauchamp & Childress 2013).

VI. Co-authored publications on DBS-associated changes in selfhood and identity

In addition to possible changes in behaviour and personality observed in studies reviewed in the previous section, postoperative DBS self-estrangement has been substantially reported by Gilbert et al. (2017). Since I have contributed to this project, a copy of the manuscript is included in this section and can be found in pages 68 to 82. In this qualitative study, we demonstrated that there are different kinds of self-estrangement experiences. We found that 47% of the people implanted with DBS for PD (8/17 interviewees) reported either a single segment, intermittent episodes, or a persistent state of self-perceived changes following implantation, even in cases of substantial motor improvements. We noted that the way patients perceive themselves through the pathology will likely influence the way they will experience potential DBS-induced self-estrangement, with those feeling more estranged by

PD also experiencing the greatest degree of self-estrangement post-DBS. In addition, the notion of self-estrangement appears to exist in association with loss of control and distorted perception of capacities. “Loss of control”, commonly manifested in inability to properly control emotions or a change in character as described by other people, is mostly associated with a deteriorative sense of the self. On the other hand, a “distorted perception of capacities” is largely related to a restorative one as evidenced by increase in self-confidence, feelings of self-rejuvenation, and heightened sense of strength and physical capabilities (Gilbert et al. 2017).

Results from our study (Gilbert et al. 2017) could be used to inform prospective participants of DBS trials on associated risks, particularly those that extend beyond the effects of DBS surgery and stimulation to the body and to the symptoms of the condition. These results could also be used to inform future researchers on what outcomes should be included in assessing DBS trials and on how the possibility of self-estrangement occurring (particularly those that are perceived negatively by the participant and his/her family) should be utilised to design strategies that would minimise harms from feelings of restorative or deteriorative estrangement.

One of the participants in our study (Gilbert et al. 2017) has been followed up further, and narratives on how she integrated the changes in her personality, preferences, and psychological state into her self-concept are described in the paper of Gilbert and Viaña (2018). This paper is also included in this section and can be found in pages 83 to 94 Mainly, we present the case of a 46-year old woman with PD who received DBS and experienced depression, mania, impulsivity, and hypersexuality afterwards. Eventually, her therapeutic

relationship with her neurologist and surgical team broke down. She also divorced her husband, moved to another Australian state, and attempted suicide. Later on, she started coping with the psychologic and psychiatric changes, indicating that she worries less; and she even started using her perceived improvement in sensory capacities (particularly, visual and auditory) to create coloured paintings expressing her emotions. What is quite striking in this account is that the patient emphasized that she was not adequately informed by the medical team of potential DBS-associated psychosocial effects (Gilbert & Viaña 2018). Our study emphasizes the importance of acknowledging patient perspectives in terms of assessing DBS-associated psychologic and psychiatric sequelae, with these perspectives potentially shedding light on socio-environmental factors that could trigger psychiatric events and ways in which a person experiencing these unintended effects copes with them. The statements of the patient regarding the informed consent process for DBS therapy also underscores the importance of adequately informing patients not just of medical risks of a particular procedure, but also of the possible psycho-social risks, especially if information on those is available in the literature. It is also vital to have a bi-directional discussion with patients to determine what risks they are most worried about in order to devise in advance coping strategies should any of these unintended sequelae arise.

Overall, sections V and VI of Chapter 3 present a number of cases wherein changes in character, behaviour, personality, preferences, and/or self-perception post-DBS have led to personal, relational, and/or social adjustment difficulties and issues. These sections do not aim to review all the literature on DBS-related psychiatric and psychological changes; rather, by providing a sample of reported DBS-associated changes, they aim to provide frames of reference on what could arise in people with AD participating in DBS clinical trials. The ethical

implications of these effects on the informed consent procedure and general conduct of DBS trials involving people with AD will further be explored in Chapter 6 (Viaña & Gilbert 2018).

The following papers have John Noel M. Viaña as a co-author and thus, are included in this doctoral dissertation:

Pages 68 to 82:

Gilbert, F, Goddard, E, **Viaña, JNM**, Carter, A & Horne, M 2017, 'I Miss Being Me: Phenomenological Effects of Deep Brain Stimulation', Originally published in the *American Journal of Bioethics Neuroscience* by the *Taylor & Francis Group*, vol. 8, no. 2, pp. 96-109. doi: 10.1080/21507740.2017.1320319. Available from: https://www.tandfonline.com/doi/full/10.1080/21507740.2017.1320319

Note: In the table on page 75, the "#" for the Model of Self employed in the studies of Gilbert (2013a, 2015, 2017) indicates that no particular model of the self was advocated for, given that these studies focus more on the concept of self-estrangement from a phenomenological point of view. I would like to thank one of the examiners for clarifying what was meant by this symbol in the table.

Pages 83 to 94:

Gilbert, F & **Viaña, JN** 2018, 'A Personal Narrative on Living and Dealing with Psychiatric Symptoms after DBS Surgery', Copyright © Johns Hopkins University Press. This article was first published in *Narrative Inquiry in Bioethics* and is reprinted with permission by the *Johns Hopkins University Press*, vol. 8, no. 1, pp. 67-77. doi: 10.1353/nib.2018.0024. Available from: http://muse.jhu.edu/article/690211

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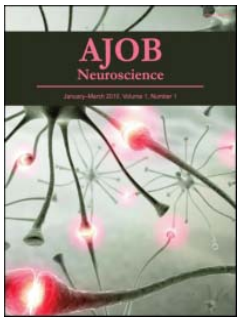

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I Miss Being Me: Phenomenological Effects of Deep Brain Stimulation

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I Miss Being Me: Phenomenological Effects of Deep Brain Stimulation

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The phenomenological effects of deep brain stimulation (DBS) on the self of the patient remains poorly understood and under described in the literature, despite growing evidence that a significant number of patients experience postoperative neuropsychiatric changes. To address this lack of phenomenological evidence, we conducted in-depth, semistructured interviews with 17 patients with Parkinson's disease who had undergone DBS. Exploring the subjective character specific to patients' experience of being implanted gives empirical and conceptual understanding of the potential phenomenon of DBS-induced self-estrangement. Our study concluded that (1) the more patients preoperatively felt alienated by their illness, the more they experienced postoperative self-estrangement, and (2) the notion of self-estrangement seems to exist in association with certain common qualitative characters, namely, loss of control, which reflects a deteriorative estrangement, and distorted perception of capacities, which reveals a restorative estrangement. These findings indicate that subjective self-reports help us to understand some aspects of the potential phenomenon of DBS-induced self-estrangement.

Keywords: alienation, deep brain stimulation, distorted perception, loss of control, Parkinson's disease, self, side effects, self-estrangement

Despite growing evidence that a significant number of patients experience postoperative neuropsychiatric changes (Volkmann, Daniels, and Witt 2010; Muller and Christen 2011, Clausen 2010), including reports of irreversible alteration following removal of implants (Gilbert 2013a), the phenomenological effects of deep brain stimulation (DBS) on the patient's self remain poorly understood and underdescribed in the literature. Most postoperative reports emerging from clinical studies measure standard cognitive, psychometric, and functional scales (Smeding et al. 2011; Lewis et al. 2015; Pham et al. 2015; Schoenberg et al. 2015). Most discussion of the postoperative changes following the implantation of brain devices such as DBS focuses on abnormal side effects caused by the intervention (e.g., hypersexuality, hypomania). By contrast, relatively little attention is paid to the idea that successfully "treated" individuals might experience difficulties in adjusting to becoming "symptom free": a phenomenon that is known as the "burden of normality" and that can lead to postoperative iatrogenic harms (Gilbert 2012; Wilson, Bladin, and Saling 2007). The risk of postoperative iatrogenic harms can be extremely serious; in a statistically significant number of clinical trials, implanted patients have attempted or died by suicide (neurological condition: Temel et al. 2009; psychiatric condition: Gilbert 2013a; Gilbert 2013b). Given the failure of studies to faithfully capture patients' experience of a "new" postoperative self, potential DBS-induced phenomenological effects on patients' self remain largely unexplored. DBS's nontarget effects and their impact on patients' self are particularly concerning, given the number of patients being implanted for approved therapy (more' than 100,000) and the increasing number enrolled in experimental trials (Medtronic 2013).

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To our knowledge, only a small number of studies in the literature have specifically addressed the phenomenology of the self through a patient's subjective experience with DBS (de Haan et al. 2015; de Haan et al. 2013, Hariz et al. 2011, Schüpbach et al. 2006). A small number of case reports provide further insight into some of these postoperative changes to the self. With so few phenomenological investigations into the experience of self, the philosophical debates about potential postoperative effects of DBS on the self are mostly based on anecdotal cases that may not be representative, but are used to serve authors' arguments. It is essential to supplement the current literature with more rigorous empirical studies exploring the phenomenological effects of DBS on the self. Studying patient's first-personal experience of DBS through the unique phenomenological lens to explore patient's self-perception will shed light on current philosophical disputes, but most importantly, will guide prospective patients through decision-making processes leading to implantation.

To address this lack of phenomenological evidence, we conducted in-depth, semistructured interviews using open-ended questions with 17 patients with Parkinson's disease (PD) implanted with DBS in Australia, from the states of Victoria, Tasmania, and Queensland.[1] The average duration of the interviews was 45 minutes. This qualitative approach allowed us to capture first-personal perspectives that are not identified by standardized questionnaires and scales. Three independent researchers conducted the interviews and transcribed the content. All interviews were conducted in English. Interviews were analyzed by grouping patients' self-experience into four main phenomenological clusters of experience: (1) degrees of alienation caused by PD or benefit caused by PD; (2) postoperative feelings of enablement or powerlessness; (3) postoperative feelings of embodiment or disembodiment; and (4) reports of postoperative changes by partner/family members. These clusters were then divided by subthemes, which were populated by patients' key answers and quotes. Table 1 reports patients' details, and Appendix 1 is the semi-structured questionnaire used to guide our interviews. Our aim was to explore perceptions of self-change by patients implanted with DBS. As this is a qualitative study based on first-personal narratives involving more than 765 minutes of interviews, the results are highlighted and given in excerpt format.

This article (1) reports our general findings; (2) reports and discusses findings related to deteriorative and restorative self-estrangement; (3) discusses embodiment through patients' accounts of experiencing DBS implants as being part of them; (4) summarizes the notion of self-estrangement; (5) advocates that DBS alone does not directly causes potential self-estrangement; (6) indicates some limits of our research; and (7) provides general conclusions from our collected data.

PATIENT SUBJECTIVE ACCOUNTS: EXPERIENCING SELF-ESTRANGEMENT

Before reporting our results, we need to define some terminology. Exploring the phenomenon of DBS postoperative self-estrangement involves an examination of whether experiencing self-estrangement involves certain qualitative experiences as phenomenally characterized by implanted patients. From a phenomenological perspective, if we define the self as, broadly construed, the subject of one's phenomenological experience of X (e.g., X being an emotion, perception, thought, etc.), then we understand that the very existence of some particular phenomenological experiences can qualitatively reflect the self. By experience, as Strawson formulated it, we understand experiential "what-it's-likeness" (Strawson 2011).[2] The existence of a self qualitatively experiencing X is given with the existence of experiencing X. In other words, experiencing DBS likely entails specific or common qualitative experiences; we aimed to explore these specific or common DBS-related experiences, especially any experiences of estrangement. By looking at the subjective character specific to patients' experience of being implanted, especially through phenomenological experience of first-personal or subjective change, we believe we can gain better empirical and conceptual understanding of the phenomenology of potential DBS-induced self-estrangement.

Our study reveals that there is a strong correlation between postoperative estrangement and how patients preoperatively perceive themselves with respect to their illness. In other words, 100% of patients who perceived PD as not intruding on their life did not experience feelings of estrangement ($n = 4$). For instance, Patient 08 and Patient 12 clearly articulated this correlation:

> Patient 08: "The disease is part of me. You can't separate from the disease" and "I don't think [DBS] changed me, it hasn't changed my personality or who I am, or how I feel about myself."

> Patient 12: "[Parkinson's] is not a painful experience . . . I was able to do things and contribute to society in ways I would otherwise have been unable to do" and later pointed out that "[DBS] has not changed who I am, it's improved."

1. This study was conducted in accordance with the Tasmanian Human Research Ethics Committee regulations. Patient Consent and Minimal Risk Ethics Application Approval, entitled "H0014820 Deep Brain Stimulation and Postoperative Self-Adjustment Phenomenon," are also in compliance with the Tasmanian Human Research Ethics Committee regulations. Ethical approval was obtained in May 2015.

2. We draw on Strawson's account here in order to justify looking at the subjective experience of DBS implantation. We do recognize, however, that this is a "thin" account of the self and that Strawson's conception of phenomenology can be contrasted with a "thick" account, which takes agency and embodiment as defining of the phenomenological standpoint.

Table 1. Patients' general information.

Patient	Age (surgery)	Gender	Time span between surgery and interview	Time span between PD diagnostic and surgery
P01	64 years old	F	1 year 6 months	10 years
P02	68 years old	F	1 year	20 years
P03	68 years old	M	2 years 2 months	12 years
P04	52 years old*	F	1 year 2 months	6 years
P05	82 years old	F	3 years	12 years
P06	63 years old	M	1 year	8 years
P07	53 years old	F	4 years	9 years
P08	50 years old	M	6 years	9 years
P09	54 years old*	F	5 years	16 years
P10	58 years old	M	1 year	11 years
P11	50 years old	M	6 years	10 years
P12	66 years old	M	1 year	11 years
P13	66 years old	M	2 years	6 years
P14	40 years old	M	4 years	7 years
P15	69 years old	M	4 years	19 years
P16	**	F	3 years 6 months	**
P17	52 years old	M	5 years	8 years

*Patients had two surgeries. Patients' ages during the second surgery.
**Was not provided.

In parallel with this strong correlation between preoperative perception of oneself through disease and a sense of estrangement, we observed that patients (61%) who felt alienated by their illness were likely to experience, to various degrees and intermittently, some postoperative feelings of self-estrangement ($n = 8$). For example:

> Patient 16: "[Parkinson's disease] really takes over. . . . I couldn't work which was a big part of my identity. . . . If I didn't have the device I'd probably be dead right now" and later states "I think that [DBS] does change you as a person."

Our findings indicate that the more patients preoperatively felt alienated by their illness, the more they experienced postoperative self-estrangement. The question that needs to be addressed in the next section is how experiencing DBS self-estrangement correlates with some specific qualitative character common to some implanted patients.[3]

3. In our study all patients (4 out of 4; 100%) reporting that PD enhanced their life also reported a general feeling of postoperative self-continuity. Some patients clearly experienced the opposite (8 out of 13; 61%): namely, they self-reported how PD devastated their existence, and simultaneously reported how they experienced postoperatively various degrees, intermittences, and intensities of estrangement. For the five remaining patients (5 out of 13; 38%), their reports are too unclear to be classified. They experienced PD as intruding in their life, but didn't clearly report significant postoperative estrangement. Thus, they couldn't fit in our classification of restorative or deteriorative estrangement.

EXPERIENCING DETERIORATIVE AND RESTORATIVE SELF-ESTRANGEMENT

Our study found that postoperative self-estrangement could be phenomenally experienced as deteriorative or restorative by implanted patients. Deteriorative or restorative self-estrangement involves experiencing an involuntary shift in the qualitative character. For instance:

> Patient 04: "I can't be the real me anymore—I can't pretend . . . I think that I felt that the person that I have been [since the intervention] was somehow observing somebody else, but it wasn't me. . . . I feel like I am who I am now. But it's not the *me* that went into the surgery that time. . . . My family say they grieve for the old [me] . . ..
>
> Interviewer 2: "What have your children said to you about the difference that they've seen before and after?"
>
> Patient 04: "Yes, they said they don't recognize me."
>
> Interviewer 2: "And in what way don't they recognize you?"
>
> Patient 04: "That I am so impulsive and seem to change my mind all the time."

What characterizes Patient 04's postoperative feelings of estrangement, as in other cases, can be understood by way of the deteriorative effects on the patient's self. We believe Patient 04 mostly experienced deteriorative consequences because Patient 04's feelings of estrangement largely appear to be correlated with a radical and ongoing sense of loss of control over her previous self, which reflects an involuntary and unintentional shift in her qualitative character. For instance, Patient 04 reported developing postoperative ongoing mania (medically diagnosed),

leading to a suicide attempt, as well as a substantial increase in impulsivity. Patient 04 said, "I cannot control the impulse to go off if I'm angry." As such, these findings appear to further corroborate the hypothesis that deteriorative self-experiences seem to qualitatively characterize the notion of powerlessness (Gilbert 2013a, 2015a), often manifested through involuntary self-harming actions/behaviors and/or loss of control.

It is a common mistake to think that postoperative feelings of self-estrangement are qualitatively deteriorative. Our study exposes that although DBS diminishes symptoms and restores patients' control over their lives, more patients experienced feelings of restorative estrangement rather than deteriorative estrangement. For instance:

> Patient 13: "[DBS] has allowed me to return almost to the person I was before … It's allowed me to be what I am, rather than change what I am," but while discussing this sudden restorative feeling, Patient 13 confessed that DBS adversely resulted in intermittent uncontrollable emotional sensitivity, to the extent of experiencing "a state of hysterics … I felt like I had lost my true self, it [is] way behind me."

Patient 13's experiences of restorative estrangement seem to separate an old self (practically understood), "DBS has partly restored my autonomy," and a postoperative qualitative character of this patient's selfhood, "I had lost my true self" as a result of the disease. Patient 13's comments illustrate that restorative estrangement can come in degrees. In this respect, a patient might experience self-rejuvenation while observing an involuntary shift in some aspects of her qualitative character. Similarly:

> Patient 11 first claimed: "it wasn't so much that it changed who you are, it rather restored who you are," but he later confessed that this novel restorative empowerment originated an uncontrollable phenomenon from which he dissociated his self and does not recognize himself: "There's nothing that I can do [to stop this] 'emotional incontinence'[4] as I call it. … If I had a choice I would say, 'Look see what you can do … to stop me from doing that.' Because it does get embarrassing."

Patient 11's postoperative feelings of restorative estrangement appear to increase some restorative capacities that the patient seems to identify with as essential for his preoperative and predisease self while admitting losing control of other aspects of his postoperative self. Aligning with these feelings of postoperative restorative estrangement:

> Patient 09 stated: "I felt I was 15 years younger after the operation … I felt so strong and confident … I could do anything … I felt so good I tried to move the pool table and I ruptured the disc in my back … I blame DBS for that because I felt so good, I did something that I couldn't have done when I was 21 and I don't know why I thought I could do it when I was 54 … I was in a wheel chair for 2 months."

Patient 09 "blames" the device for her ruptured disc (i.e., she accepts it was her fault, but she attributes her unreasonable confidence to the success of the device). We observed that sometimes the device provided such levels of heightened and uncharacteristic confidence that this resulted in other unforseen difficulties. For example, Patient 06 observed that he was bold in his activities, had difficulties in refraining from engaging in numerous commitments, and that he was in conflict with his wife: "I think I have been causing a bit of problems in my relationships by being just so full on. … I have to slow down that activity and make it more manageable for myself and my wife." In a similar way, Patient 09 was so confident in her newfound strength and physical capabilities that she was nearly permanently disabled when she attempted to lift and move a large pool table. In this way, DBS may be construed as so effective in relieving symptoms that it actually causes people to have a distorted view of their own capabilities. These distorted perceptions appear to induce the belief that patients have (some) enhanced capacities far in excess of their actual abilities. These distorted views of their capacities are often described in the language of sudden unexpected strength.

For instance, Patient 07 described her feelings after suddenly acting out of character during calibration. She reported starting walking and wanting to reach her husband's location (i.e., by foot), which would have taken her days. She explained her decision later by saying:

> "Oh God, I wasn't me, and I knew I wasn't me and there was nothing I could do about it … I knew what it was! I knew [DBS] had been turned up that day. Unlike the drugs which creep up on you, and you don't know what's happening. With [DBS] I knew what it was, so I knew it was fixable."

Here again, the device is similarly "blamed" for the sudden restorative strength. The device is responsible, "I knew what it was! I knew [DBS] had been turned up that day," for the distorted interpretation of her own capacities, "I knew I wasn't [my capacities]."

In parallel, while describing a sense of loss of control, Patient 04 also recognized DBS had given her increased feelings of strength (despite having mostly suffered from deteriorative estrangement):

> "I never had felt this lack of power or this giving of power—until I had deep brain stimulation … It's like the psychologist said [to me]: for a woman who had a very invasive brain surgery nine days ago and you've just walked 10 kilometres [to get to your appointment]. And on the way I stopped and bought a very uncharacteristic dress, backless—completely different to what I usually do."

Here, Patient 04's "lack of power" in some aspects of her character seems to be replaced by a "giving of power" with respect to other novel qualitative features of character—that

4. DBS has turned Patient 11 into a SNAG (patient words), a phenomenon beyond his control and putting him in discomfort. A SNAG is an acronym for "Sensitive New Age Guy."

is, a loss of control leading to a disinhibition that is characterized by some incommensurable feelings of strength.

The collected restorative narratives seem to indicate that DBS can distort patients' feelings of who they are or make them feel like they aren't themselves in some ways, capable of reaching unwanted limits beyond the preoperative self, for instance, as well as inducing unintended estrangement experiences of being in the world.

Given the preceding discussion, our study shows that the notion of self-estrangement seems to exist in association with certain common qualitative characters: namely, loss of control, which reflects a deteriorative estrangement, and distorted perception of capacities, which reveals a restorative estrangement.

EMBODIMENT: HAVING A BRAIN IMPLANT VERSUS BEING A BRAIN IMPLANT

Another way to understand how DBS might induce feelings of estrangement is to examine whether DBS has an effect in terms of being understood as a foreign intrusion; that is, whether the patients viewed the device as being a part of, or not a part of, themselves. For instance, for Patient 08, "It's just become part of me. It's more the other way around. It's more the DBS becomes a part of who you are rather than changing you." In this case the patient identifies with or sees him- or herself as continuous with his or her stimulated self. In contrast, when the device is seen as other or an outside force, it could contribute to feelings of self-estrangement.

However, our study found that the hypothesis—that if patients incorporate the DBS device into their self-image/body schema, then they will suffer less from self-estrangement—is not as robust as it sounds. In general, the patients interviewed did not notice the device in their body while it was doing its job in the background, despite having experienced some degrees and intermittent episodes of self-estrangement. Many noted that the device had a minimal presence in their body and that they did not typically notice that it was there. For example, Patient 13 declared, "I charged *myself* up this morning"; Patient 12 asserted, "I just don't know it's there. I don't feel invaded." Patient 06 affirmed, "It's part of me." Patient 05 indicated, "More a part of my body." Such responses appear to illustrate that patients use a language that seemingly incorporates the DBS device into their self or body image. Patient 13 clearly uses such metaphorical language; he does not say "I charged the devices up this morning" but rather "I charged myself up." Such language could indicate an embodied acceptance of the implant, of patients feeling like being one with the implant.

Nonetheless, we did find a correlative example between the device felt as an alien entity and a patient experiencing self-estrangement. Patient 04, who experienced the most severe and harmful effects of estrangement in our study, declared the following in response to the interviewer's question:

> Interviewer 1: "The implant, do you feel that it is part of you?"
>
> Patient 04: " No!"
>
> Interviewer 1: "You feel that it is alien?"
>
> Patient 04: "I hate it. I wish I could pull it out!"

Aside from this obvious case with Patient 04, who clearly experienced having a foreign device rather than it being part of her (i.e., language of being the device), most patients incorporated the devices. A few complained that it hampered, or had hampered, physical activity in the past. Patient 08 said, "I used to be able to feel the electricity going through my body but I don't feel it now … I forget about it most of the time, but I am aware because there is a hard little thing on your chest." Others had (perhaps unwarranted) fears about others interfering with the device accidentally (one research participant instructed hairdressers not to use clippers on her neck in case it damaged the wires). But in general, patients seemed to regard the device as something that had been integrated into their body. Most did not view it as a foreign entity that existed separately from their own self. The fact that patients tend to forget about the DBS implant might be construed as a positive thing because, in the end, they may focus less on their disease. This perception prevents DBS from having a felt intrusive quality. An interesting general point is that patients with non-rechargeable devices seemed not to notice the device as much, and it didn't have as much presence to them. Some patients with rechargeable devices noticed it a lot more, sometimes obsessing over its charge.[5]

In addition to exploring whether and how the implant altered patients' relationship to their body, we can explore the relationship to changed capacities of the body. Patients' measure of restoration often correlated with their physical abilities, and they declared being more independent (e.g., patients 16 and 17). However, as also noted in the preceding, some patients overestimated their capacities, in some cases beyond what they were capable of prior to the stimulation and the onset of PD. These experiences were often connected with a feeling of a loss or lack of control.

SUMMARIZING DBS POSTOPERATIVE SELF-ESTRANGEMENT

Our study demonstrates that there are various qualitatively different kinds of self-estrangement experiences. To speak of a postoperative estrangement implies that

5. There were some fears concerning what would happen if the device was not charged correctly (i.e., for those with rechargeable batteries). Some research participants took a very conservative attitude toward the battery charge and constantly monitored and topped up the battery. Others were very casual and let the battery run down a lot. The people who were concerned about monitoring the charge level were also people who seemed to have some anxieties about the implications of what would happen if the device ran out of power. Those who were more casual seemed to not harbor those sorts of fears. One person accidentally turned off his device at one point and only noticed a few hours later when he had trouble typing. But it was easily remedied and the event did not bother him or give him any further anxieties.

the relevant patient experience of deteriorative or restorative estrangement has an irreducibly subjective character specific to the implanted individual (Atkins 2000). The postoperative feelings of estrangement constitute a patient's first-personal point of view of a qualitatively deteriorative or restorative experience. Experiencing deteriorative or restorative self-estrangement does not mean a subject is experiencing X differently (e.g., X being an emotion, perception, thought, etc.), but rather that the experience of being the subject of X is qualitatively different. Experiencing X differently is not the same as experiencing oneself as qualitatively different. In other words, in some cases, the experience of X can feel different while the experiencer remains identical. Accordingly, an experiencer can feel estranged while the experience of X feels identical in some cases. In that respect, being self-estranged cannot be reduced to experiencing X differently; it rather involves an irreducibly novel experience of being the subjective character of X (experiencer is necessarily qualitatively different, but not necessarily X). Being a subject of X does not involve estrangement when the subjective experience is identical.

DBS ALONE DOES NOT DIRECTLY CAUSE POTENTIAL SELF-ESTRANGEMENT

There is a lack of consensus about how to adequately characterize the self vis-à-vis DBS treatment within the neuroethical literature. The current state of the debate is eclectic. Table 2 shows the numerous theoretical models of the self motivated to explain the effects of DBS on the self, including, but not limited to, the self as characterized by "self-representational capacities" (Synofizik and Schlaepfer 2008); as a "foundational-functional model" (Witt et al. 2013); as narrative self-constitution (Schechtman 2010) or relational narrative constitution (Baylis 2013); as an "enactive, affordance-based model" (De Haan et al. 2013); and as a "pattern theory of self" (Dings and de Bruin 2015). In addition to various models of the self, there is disagreement about the central concept affected by DBS, autonomy, and/or identity, and how to characterize these effects—for example, autonomy in terms of patient autonomy or competence, loss of control, and identity in terms of changes to personality or psychological continuity, to name a few. The conceptual understanding of agency also varies in these accounts. Most philosophical discussions concerned with potential DBS-induced effects on the self are not based on firsthand studies (see Table 2).[6] Also, when examining the firsthand studies from which the philosophical debate is inspired, we quickly observe that these studies describe a wide range of anatomical targets, as well as a diversity of unwanted personality changes associated with postoperative DBS intervention.

Further, there is a potential to claim that DBS directly causes these changes. It is often inferred in the nonscientific literature that DBS intervention poses a postoperative threat to personal identity, or induces some unwanted personality changes or has an unintended effect on the self. For instance, some have written, "The risk of becoming another person following surgery is alarming" (Witt et al. 2013) and "personality changes represent a threat to personal identity and agency" (Schechtman 2010). We categorize these positions as a "post hoc ergo propter hoc"-related assumption. Many neuroethical and philosophical documents[7] are guilty of perpetuating this assumption with little examination or scrutiny.

What do subjective self-reports from PD patients with DBS show us about the potential for self-estrangement? Our study found that 8 patients among 17 (47%) experienced some degrees of, and intermittent episodes, of self-estrangement. These results align with clinical reports, which indicate that the phenomenon of "becoming a different person" after DBS intervention may not be solely attributed to the electrical stimulation itself but could be caused by treatment adjustments post surgery or by disease progression (Volkmann, Daniels, and Witt 2010). As such, the prevalence and incidence of self-estrangement might not be exclusively correlated with a specific DBS target and/or stimulation parameter but rather should be seen as a result of the interaction between the neural and glial effects of electrode insertion during surgery (Vedam-Mai et al. 2012) and electrical stimulation, adjustments in medication, and natural progression of the disease (Volkmann, Daniels, and Witt 2010), especially when DBS is used in patients with neurodegenerative disorders where changes to personality and identity are inevitable regardless of treatment course and choices. Although DBS affects spiking activity and neurotransmitter release in local (Hammond et al. 2008; Cheney et al. 2013) and distant circuits (Li et al. 2014), turning off stimulation won't conclusively allow dissociation of personal identity changes as a result of electrical stimulation from DBS and as a result of associated treatment modifications and disease prognosis. This is further complicated by the potential of DBS to induce long-term synaptic changes in the brain (Herrington, Cheng, and Eskandar 2015). However, some case reports do seem to suggest that turning off the stimulation ends, for instance, an episode of mania or impulsivity (Tsai et al. 2010), and if longer term synaptic changes are made, then we might not expect the personality changes to disappear with the removal of stimulation (Gilbert 2013b). Overall, changes in identity, personality, and self-awareness during DBS not only should be attributed to the DBS target structure, surgical trajectory, and stimulation

6. We do not have enough space to adequately characterize the accounts in Table 2 concerning the potential DBS-induced effects on the self. Rather, we aim to examine a patient's postoperative phenomenological experience of first-personal or subjective change, especially responses, or feelings of, self-estrangement.

7. Though not necessarily all those listed in Table 2.

Table 2. Survey of the existing model of DBS-induced effect on the self.

Central concept of ethical significance given impact of DBS	Discussed by	DBS impacts characterized by	Quote	Model of self
Autonomy and related concepts	Synofzik and Schlaepfer (2008)	The "level" and "extent" of changes to naturalistic notion of personality	"The ethically decisive question is not whether DBS alters personality or not, but whether it does so in 'a good or bad way' from the patient's very own perspective." (1514)	Naturalistic model of self as the "objective, biological-cognitive representational system with special characteristic self-representational capacities" (1513)
Autonomy and related concepts	Schermer (2011)	Perceived changes to narrative identity	"[W]hether or not the patient himself perceives the changes in his personality, mood, behavior, or cognition brought about by DBS as disruptive of his personal narrative identity." (2)	Narrative identity
Autonomy and related concepts	Gilbert (2013a, 2015, 2017)	Loss of control and powerlessness	"Postoperative self-estrangement may enhance or restore one's control over one's life or illness. However, in some cases, DBS radical modifications of the self may lead to a loss of control or experiencing feelings of powerlessness." (109)	#
Autonomy and related concepts	Mackenzie and Walker (2015)	Autonomy competence	"This distress, in our view, points to threats to autonomy rather than to identity or authenticity, as the salient concern underlying narratives of self-alienation." (390)	Relational, narrative understanding of identity and autonomy
Authenticity and related concepts	Johansson et al. (2011)	Personality changes and impacts on authenticity	"The concept of authenticity . . . provides a means to entangle both philosophically and generally held intuitions regarding normative claims connected to personality changes." (2)	Normative thesis of authenticity

Authenticity and related concepts	Kraemer (2013)	Felt-authenticity and felt-alienation	"For some, alienation can be brought about by neurointerventions because patients no longer feel like themselves. But, on the other hand, it seems alienation can also be cured by DBS as other patients experience their state of mind as authentic under treatment and retrospectively regard their former lives without stimulation as alienated." (483)	Identification/endorsement with felt-authenticity and felt-alienation
Identity and related concepts	Gisquet (2008)	Changes in personality and loss of control over managing one's life and illness	"Cerebral implants are a unique form of biographical disruption . . . [T]he patient loses control over managing the illness and experiences significant changes in personality." (1850)	Biographical
Identity and related concepts	Focquaert and De Ridder (2009)	Changes in personality and self-perception	"Neuromodulation via implanted electrodes can influence narrative identity directly and indirectly." (2)	Narrative identity
Identity and related concepts	Glannon (2009)	Changes in thought and personality	"Stimulating the brain . . . may alter a range of mental states critical to thought, personality and behavior. This can disrupt the integrity and continuity of the psychological properties that constitute the self and one's experience of persisting through time as the same person" (289)	Narrative identity
Identity and related concepts	Klaming and Haselager (2010)	Disruptions of psychological continuity impact on patient competence and responsibility	"DBS may . . . influence mental states critical to personality to such an extent that it affects an individual's personal identity . . .. [This] raises a number of ethical and legal questions. . . . [I]nduced changes . . . [may] result in damage caused by undesirable or even deviant behavior. Disruptions in psychological continuity can in some cases also have an effect on an individual's mental competence." (527)	Psychological criteria of personal identity

(*Continued on next page*)

Table 2. Survey of the existing model of DBS-induced effect on the self. ***(Continued)***

Central concept of ethical significance given impact of DBS	Discussed by	DBS impacts characterized by	Quote	Model of self
Identity and related concepts	Witt et al. (2013)	Patient's core attitudes	"Ethical evaluation of deep brain stimulation as treatment for Parkinson's Disease is complicated by results that can be described as involving changes in the patient's identity. The risk of becoming another person following surgery is alarming for patients, caregivers and clinicians alike." (499)	Foundational-function model: self as a set of core attitudes
Identity and related concepts	Mecacci and Haselager (2014)	Psychological maladaptations and conceptual schemes concerning the relationship between mind and brain	"We hypothesize that the frequently reported maladaptations might be partially caused by a conceptual emphasis on 'braincentric' materialism." (31)	Embodied embedded stance toward the mind–brain relationship
Identity and agency	Schechtman (2010)	Narrative identity and agency/disruption of the narrative flow	"Stimulation-related psychological and personality changes represent a threat to personal identity and agency." (133); "DBS can pose a threat to identity by threatening narrative." (139)	Narrative self-constitution
Identity and agency	Baylis (2013)	Disruption of the balance between how a person sees and understands herself and how others see and understand her	"From the perspective of relational personal identity, when DBS dramatically disrupts the narrative flow, this disruption is best examined through the lens of agency." (514)	Relational narrative identity
Identity and agency	Lipsman and Glannon (2013)	Personal identity and a sense of free agency	"Brain implants . . . have significant implications for what it means to persist as the same person and be the source of one's thoughts and actions." (465)	Neurobiology of identity (narrative and numerical) and identification (Frankfurt)

Identity and agency	Dings and de Bruin (2016)	Aspects of the self—embodied, experiential, affective, intersubjective, psychological/cognitive, narrative, extended, and situated	"Our aim in this paper is to develop a pattern theory of the self, and to explain how this theory can be applied at the level of pattern types and pattern tokens." (fn 8, 158)	Pattern theory of self
Identity and agency	De Haan et al. (2013; 2015)	Patients experience a richer field of affordances and act more flexibly on these new affordances	"It turns out that patients may experience profound changes as the result of DBS treatment. It is not just the symptoms that change; patients rather seem to experience a different way of being in the world." (2013, 1)	Enactive, affordance-based model

parameter, but also should account for patient history, disease attributes, and other forms of treatment adaptations such as medication adjustments and psychotherapy.

At this point in time, it is relatively difficult to isolate the cause of these postoperative changes, though they have been associated with DBS. To the best of our knowledge, no neurobiological studies claim that postoperative personality changes can be predicted solely on the basis of DBS itself or an exclusive neurobiological cause. Even in a tragic case where a patient implanted with DBS died by suicide, an indirect causal explanation was used in the legal case to argue that postoperative changes are "more likely than not to have been due in significant but unquantifiable measure to the DBS" (Dillon 2014).

A similar relationship is seen in Parkinson's disease patients who develop compulsive behaviors or impulse control disorders (ICD) (e.g., compulsive gambling, shopping, and eating) associated with dopamine replacement therapy. As seen during our interviews, many patients reported self-changes due to medication. This correlates with other findings that show that almost 17% of individuals with PD who are treated with dopamine agonists (DA) will develop an ICD (Ambermoon et al. 2011). There is strong evidence that DA plays an important causal role: These behaviors tend to emerge soon after commencing the medication or increasing doses, and they often resolve when the medication is stopped, as some of our patients reported. There is also a plausible explanation for how dopaminergic medications would lead to compulsive behaviors. The medication only plays a partial causal role: the overwhelming majority of individuals do not develop these disorders. There are also predictable individual differences that identify the likelihood of developing a compulsive behavior, such as having a personal or family history of addictive or impulsive behavior. The sorts of behaviors that emerge appear to be heavily influenced by social factors: Women tend to engage in compulsive shopping and eating, while men are more likely to develop pathological gambling or hypersexuality.

In short, this work does not advocate that DBS alone directly causes potential personality changes.

LIMITATIONS OF THE STUDY

There are a number of limitations in this study. It is important to clarify what the study was, and was not, doing. There is concern with the lack of data concerning first-personal phenomenological reports or assessments of neural implants, which this article in some sense seeks to address. Connected to this point is the concern that no generalizable conclusions can be drawn from such limited data. While looking at the phenomenology of DBS might be a useful tool for describing the lived experiences of implanted patients, it remains severely impoverished as a theory for explaining it (Sholl 2015). However, we are not attempting to draw generalizable conclusions on the basis of numbers, but rather, we aim to examine phenomenological first-personal reports to inform understandings of the impacts of DBS on patients' self, with a focus on self-estrangement.

First, it should be recognized that drawing on subjective or first-personal phenomenological accounts of how a person feels about or experiences their implant does not provide us with enough context to assess the (objective) accuracy of these accounts. Estrangement is not necessarily self-perceived. As other studies have demonstrated, relatives are often more sensitive to alterations in self than the patients themselves (Pham et al. 2015). In addition to what we discussed in the previous section, Patient 03 reported, "I don't feel different at all. Some people said to me that I am a bit different." Correspondingly, Patient 06 reported, "I think I have been causing a bit of problems in my relationships." Also, the epistemic role of the first-personal perspective may be limited, particularly in the case of induced mania. We are not questioning the what-it's-likeness but rather the consistency of the narration. As family members pointed out to Patient 04, "They said they don't recognize me . . . I am so impulsive and seem to change my mind all the time." Here it is not the experiential-qualitative character of being manic which is problematic, but rather the consistency of the narrative account. Families and social context are an essential measurement of how patients are experiencing potential estrangement, even if patients do not perceive it. An extended study would not only involve interviewing the implanted patients, but also their close relatives. In the current study, patients were asked whether their relatives mentioned any postoperative changes, but systematically interviewing patients' relatives would have likely generated more data.

Second, and more importantly, our study merely asked patients to report on their perception of self-change. As such, it provides a limited amount of information about patients' uptake and adaptation over time. As such, there is insufficient evidence to draw conclusions about how the implants affect autonomy and identity and consequently to draw conclusions about the impacts on autonomy and identity. An extended version of the study should also include interviews made before the intervention, and at least two follow-ups; this would add important insights regarding the degree of "self-deception" of patients when remembering their state prior to surgery. Further, the study should include focus on the patient's engagement with the world and his or her implant, in addition to reporting on perception of self-change.

Despite these identified limitations, we strongly believe that we can draw some robust and common findings from the patient postoperative narratives, as we have done in the preceding, and on the basis of these findings make some conclusions, as summarized in the following. Further, exploring patient's first-personal experience of DBS can inform and guide patients through decision-making processes leading to implantation, and can also answer questions of patients currently experiencing self-estrangement phenomenon.

CONCLUSIONS

Subjective self-reports from PD patients with DBS help us to understand some aspects of potential postoperative self-estrangement. The way patients perceive themselves through pathology will likely dictate the way they will experience potential DBS-induced self-estrangement; self-perception through pathology will likely dictate degrees of whether patients self-perceive DBS as something that is restorative. The notion of self-estrangement seems to exist in association with certain common qualitative characters: (1) loss of control and (2) distorted perception of capacities. The first is mostly associated with a deteriorative sense of the self, and the second is largely related to a restorative one. Most implanted patients we interviewed experienced a shift in their self-perception, mostly in a restorative sense, especially during calibration. Some feelings of deterioration were experienced in relation to powerlessness, which resulted in severe harm in one case. This evidence supports the hypothesis that postoperative feelings of powerlessness play a crucial role in causing harm (Gilbert 2013a, 2015a). This study demonstrates that DBS, as a whole, increases autonomous restorative power over one's self, rather than a deterioration of the self. This is anecdotally supported by our interviews with patients who reported a sensation of empowerment. The explanation for this may reside in the concept of embodiment, where the device is felt to become part of the individual, rather than as a foreign despot exerting control (Amadio and Boulis 2015).

It appears from these clusters that most patients experience a proportionally restorative sense of the self. This evidence justifies the claim that, generally speaking, DBS is not a threat to personal, but some patients might not experience well any form of estrangement. Patients would benefit from being informed ahead of any potential risks, prior to consenting to being implanted, as in other types of invasive brain intervention (Viaña, Vickers et al. 2017; Gilbert et al. 2014; Viaña, Bittlinger et al. 2017; Gilbert 2015b; Bretzner et al. 2011; Gilbert, Vranic, and Hurst 2013; Gilbert 2014; Gilbert et al. 2015; Vranic & Gilbert 2014; Gilbert & Cook 2015; Gilbert 2017; Gilbert & Dodds 2013; Gilbert & Focquaert 2015; Gilbert & Vranic 2015).

This study highlights the importance of the first-personal perspective and subjective assessments when considering the impacts of implants and the need for more assessments. More significantly, however, we argue that further and more fuller phenomenological exploration of how patients respond to their neural implants is needed in order to draw conclusions about the impacts of DBS on autonomy and identity. This would involve interrogating patients' agency over time so that we can make an assessment of whether initial disruptions, feelings of self-estrangement, and failures in decision making are short-term or long-term phenomena. Furthermore, this would involve assessing how patients live with their implants, with a focus on whether the implant facilitates or hinders their capacities to engage in the world.

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APPENDIX: SEMISTRUCTURED INTERVIEW SCRIPT

These are examples of generic questions. They are an indication of the structure to be followed during the interviews, rather than the actual questions to be asked to patients. The choice of words, terminology, or languages may change slightly for each patient.

1. Potential questions regarding postoperative sense of the self.
   i. What was it like to live without the deep brain stimulation (DBS) device? Did you feel comfortable in yourself with your medical condition? How did you feel that your medical condition affected your life?
   ii. What is it like to be implanted with DBS? Do you feel any significant difference from before the device compared to after it was implanted?
      - Please provide some examples. Did you expect to find differences or changes prior to the operation?
   iii. Have others commented on any changes to you (e.g., personality, habits, etc.) since being implanted? If so, do you agree with them? Why or why not?
   iv. (Depending on previous answers) Do you think you may change/change more in the future as a result of this intervention?
2. Potential questions regarding the sense of control.
   i. Prior to the implantation of DBS, how would you describe your control over your life? (e.g., through habits, daily activities, etc.)
   ii. Do you feel the device has increased your autonomy (e.g., making you less dependent on others)? For instance, has it improved your life, control on symptoms? Has it given you back more control over your life?
   iii. Have others commented that you have better control over your life/symptoms/yourself? Do you agree with them? If not, why not?
   iv. (Depending on previous answers) If you experienced the device as form of control, does it feel authentic? From your own personal experience, do you see it as a novel control?

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CASE STUDY

A Personal Narrative on Living and Dealing with Psychiatric Symptoms after DBS Surgery

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Abstract. Although deep brain stimulation (DBS) may result in dramatic motor improvement in people with Parkinson's disease (PD), it has been correlated with a number of postoperative psychiatric side effects. We report a case of a person with PD experiencing depression and hypomania following DBS surgery. We provide a detailed report of the patient's personal experiences dealing with and managing these psychiatric side effects for three years. Providing a personal narrative focusing on detailed patient subjective experiences complements reports that give insight into the short- and long-term effects of DBS on established psychiatric measures and neurologic activity. But, most importantly, such a qualitative approach provides prospective patients and clinicians with a broader ethical picture of real-life challenges faced and coping strategies employed by PD patients treated with DBS who are experiencing psychiatric adverse events. This case study reinforces the ethical need to disclose the potential risk of harm to prospective patients as well as the importance of establishing a multidisciplinary postoperative supportive group.

Keywords. Deep Brain Stimulation, Identity, Neuropsychiatric Effects, Parkinson's Disease, Self, Side Effects.

Introduction

Deep brain stimulation (DBS) has been regarded as an efficient and safe treatment for Parkinson's disease (PD) for the last 25 years (Schultz, 2002). During this time, several thousands of people with PD have received DBS therapy. In terms of clinical ethics, it is worth asking whether the use of DBS may have unanticipated negative effects similar to those associated with other types of neurosurgery: in particular, how postoperative neuropsychiatric effects may impact upon a patient's sense of self (Gilbert, Cook, O'Brien, & Illes, 2017; Gilbert,

Goddard, Viaña, Carter, & Horne, 2017; Gilbert, Vranic, 2015; Gilbert, Harris, Kapsa, 2014). In some instances, symptoms are alleviated but patients do not cope well with their new "normal" life, a syndrome known as the "burden of normality" (Gilbert, 2012).

Potential adverse effects of DBS raise important ethical concerns. Unlike the side effects of drugs that may simply require stoppage of intake or decrease of dosage to be controlled, DBS is an invasive procedure that necessitates risky interventions for removal from the body. Most importantly, turning stimulation down may not actually alleviate side effects; indeed, studies have shown that calibrating stimulation has induced worst adverse effects for some patients, including suicide attempts (Gilbert, 2013a; 2015a). As a result, DBS adverse events may increase the magnitude of harm to patients, especially if the intervention appears to be correlated with postoperative effects involving the core components of a patient's personality: self and identity.

The phenomenological effects of DBS on patients' postoperative existence remain poorly understood. Some researchers suggest that the impact of DBS on patient personality is characterized by self-perception through narrative identity (Focquaert & De Ridder, 2009); changes in thought and personality (Glannon, 2009); disruptions of psychological continuity influencing competence and responsibility (Klaming & Haselager, 2010); alteration of a patient's core attitudes (Witt, Kuhn, Timmerman, Zurowski, & Woopen, 2013); variation in embodied, affective, intersubjective, cognitive, narrative, extended, and situated aspects of the self (Dings & de Bruin, 2016); or changes in relational autonomy competences (Brown et al., 2016). We do not have enough space to characterize all accounts adequately, but it appears that DBS may lead to some existential side effects that are ostensibly profound, as patients may experience shifts in identity in relationship to both themselves and their families.

Most studies on the psychiatric adverse events caused by DBS in PD patients focus on its effect on several established psychological tests and psychiatric measures in a number of individuals over time (Castrioto, Lhommée, Moro, & Krack, 2014; Boel et al., 2016), with a few investigating the effect of stimulation on brain activity (Ulla et al., 2011). Although some publications present case reports, providing brief descriptions of the progression of the experienced psychiatric symptoms with respect to adjustments in medication and stimulation parameters (Funkiewiez et al., 2004; Rodrigues et al., 2010; Ugurlu, Acar, Karadag, & Acar, 2014; Widge et al., 2013), or statements from patients and caregivers (Lewis et al., 2015), they do not really provide detailed long-term information on patients' subjective experiences before symptom onset and potential socioenvironmental factors that could have triggered or exacerbated these symptoms, patient perspectives while experiencing psychiatric conditions, and coping strategies that patients potentially employ in addition to medication and stimulation adjustments. This presents a gap in the literature on DBS-associated psychiatric adverse events from patients' points of view, information that that would also be important in understanding how these events affect actual patient day-to-day experiences and perceptions of DBS therapy.

In this study, we report on the case of a patient with PD exhibiting depression and hypomania after DBS, despite improvement in motor symptoms. We detail the patient's personal experiences with these psychiatric adverse events and the ways in which she experienced them. These qualitative accounts provide a perspective beyond standard psychological tests, psychiatric evaluations, and neurologic measurements on neuropsychiatric issues in DBS for PD by highlighting a PD patient's perception of life with these symptoms and providing prospective patients and clinicians a more detailed, relatable, and empathic understanding of these issues through the narration of our case subject's experiences of struggle, acceptance, and recovery. This case illustrates an ethical concern, in that successful postoperative alleviation of motor symptoms did not necessarily result in an improvement in the patient's overall well-being.

Case Report

A 46-year-old female patient, with no history of mental health issues, underwent bilateral subthalamic nucleus (STN) DBS in August 2013. She consented to DBS surgery 6 years after receiving a diagnosis of PD and being refractory to the most common drugs (dopamine agonists). Following DBS surgery, Parkinsonian tremor remained substantial, which required adjustment of stimulation parameters. Calibration resulted in significant diminution of motor symptoms; however, concomitant psychiatric symptoms emerged, in particular depression and mania, for which Zoloft and Seroquel were prescribed. In the following months, the patient experienced a wide range of feelings, especially intense distress, which were articulated through various narratives. Subsequently, her therapeutic relationship with her neurologist and surgical team broke down. Successively, she divorced the father of her children, moved to another state, and ultimately attempted suicide in February 2014.

The patient was included in our multicentre qualitative postoperative study of DBS for PD. We used qualitative methodological tools to conduct continuous in-depth, semistructured interviews using open-ended questions in order to understand PD patients' perception of self-changes following surgery (Gilbert, Goddard, Viaña, et al., 2017). This qualitative approach gave us access to first-person perspectives that are not captured by standardized questionnaires and scales.

The patient reported a persistent state of self-perceived changes following implantation. More than one year after surgery, her narratives explicitly refer to a persistent perception of strangeness and alteration of her concept of self. For instance, she reported:

> can't be the real me anymore—I can't pretend . . . I think that I felt that the person that I have been [since the intervention] was somehow observing somebody else, but it wasn't me. . . . I feel like I am who I am now. But it's not the me that went into the surgery that time. . . . My family say they grieve for the old [me]. . . .

In another occurrence, when discussing her divorce and the rupture in her familial structure, she reported how her children perceived her postoperative self:

> *Patient:* My family say they grieve for the old [me] . . .
> *Interviewer:* What have your children said to you about the difference that they've seen before and after?
> *Patient:* Yes, they said they don't recognize me.
> *Interviewer:* And in what way don't they recognize you?
> *Patient:* That I am so impulsive and seem to change my mind all the time. . . .

The patient also reported developing severe postoperative impulsivity: "I cannot control the impulse to go off if I'm angry." In parallel, while describing a sense of loss of control over some impulsions, she has also recognized that DBS gave her increased feelings of strength: "I never had felt this lack of power or this giving of power—until I had deep brain stimulation." Here, the patient's "lack of power" in some aspects of her character seems to also result in a "giving of power" in other novel qualitative features of character; that is, a loss of control leading to a disinhibition has also given her some incommensurable feelings of strength. For instance, she experienced radically enhanced capacities, in the form of increased uncontrollable sexual urges:

> I know this is a bit embarrassing. But I had 35 staples in my head, and we made love in the hospital bathroom and that wasn't just me. It was just I had felt more sexual with the surgery than without.

And greater physical energy:

> I remember about a week after the surgery, I still had the 35 staples in my head and I was just starting to enter the cooler months of winter but my kids had got me winter clothes so I had nothing to wear to the follow up appointment and when I went back there of the morning, I thought "I can walk into the doctor's" even though it was 5 kilometers into town. It's like the psychologist said: "For a woman who had a very invasive brain surgery 9 days ago and you've just almost walked 10 kilometers." And on the way, I stopped and bought a very uncharacteristic dress, backless—completely different to what I usually do.

Figure 1. A colored painting made by the patient.

In the following interviews, the patient's experience of being estranged from her previous self was different; in particular, when the treating psychiatrist tried calibrating the DBS parameters:

> I went to the psychiatrist, and he said, "Right, well, this is bordering on mania, you need to turn the settings right down to manage it." I said to him, "Please don't, this is not over the top—this is just joy."

Eventually, the patient's narrative started to indicate progressive coping with postoperative psychiatric changes:

> Well, it was different to—I've always been a worrier for so many years. Now, I don't seem to have that worry thing anymore . . . I feel that other [me] that was before the surgery would never have able to stand on her own two feet. . . . I wouldn't [have] been able to cope if I was the old [me]."

To some extent, the patient started to use her new postoperative capacities. She started expressing her emotion through colored painting (Figure 1) and is currently selling some of her creations.

> I don't know, all the senses came alive. I wanted to listen to Paul Kelly and all of my favorite music really loud in the toilet. And you know, also everything was colourful. . . . Well, since brain surgery I can. I didn't bother before. I can see the light . . . the light that is underlying

> every masterpiece in photography. . . . I've seen it like I've never seen it before . . . I am a totally different person. I like it that I love photography and music and colourful clothes, but where is the old me now?

The patient still faces challenges linked to her new self, but she has developed an attitude to embrace several aspects of it:

> *Interviewer:* And over this subsequent 2 years, you've come to actually feel that rather than being self-estranged, you are actually truly who you are—is that correct?
> *Patient:* Yes.
> *Interviewer:* Would you go back to the old [you] if you could?
> *Patient:* No. . . . I don't have any regrets about who I am now. But I have regrets, and I'm not angry anymore—just concerned that I wasn't given the opportunity to know what could possibly happen.

A surprising element we observed is that on many occasions, the patient mentioned and maintained that she was never informed by her initial medical team about potential unwanted psychosocial effects of the treatment.[1]

Discussion

There is an ongoing debate in the literature about the clinical and ethical implications of personality changes following DBS surgery. This debate discusses trade-offs between the motor benefits of DBS and the potential psychological harm caused by the intervention. The discussion often addresses the issues of how the medical team should account for personality changes (de Haan, Rietveld, Stokhof, & Denys, 2013), whether patients should be prescribed deactivation or explantation (Gilbert, 2015a), and what moral criteria could guide a patient's decision to accept side effects while enjoying motor symptom alleviation (Glannon, 2009). Our case raises ethical difficulties because it illustrates how DBS treatment may result in unexpected outcomes for patients along with a diminution of targeted symptoms, even after many years of follow-up. As a result, the ethical question of benefits and risks associated with DBS treatment is raised. The potential psychosocial risks demonstrate that access to information with respect to potential unwanted DBS-induced effects is an ethical priority. Clinicians should prioritize appropriately informing prospective patients, their families, and their caregivers about treatment responses that might not be in line with the therapeutic goals of the DBS intervention. Access to information should also highlight the limits of the treatment and its potential long-term psychosocial effects, despite diminution of the illness's core symptoms. It is fundamental to stress these details, as our patient reported never having received information on potential unwanted psychosocial effects of the treatment from her initial medical team.

The observed psychiatric side effects in the case reported here are not the first of their kind and have also been observed in other PD patients who underwent STN DBS. Depression (Anderson & Mullins, 2003), mania (Ugurlu et al., 2014; Chopra et al., 2012), aggression (Sensi et al., 2004), and impulsivity (Hälbig et al., 2009; Ballanger et al., 2009) have all been observed in a number of patients. Such effects can be due to the stimulation itself or accompanying medication changes and can also be influenced by preoperative psychiatric history (Anderson & Mullins, 2003; Witt, Daniels, & Volkmann, 2012). Moreover, the postoperative development or progression of these psychiatric side effects varies, with some patients reporting improvement and others worsening (Castrioto et al., 2014; Anderson & Mullins, 2003; Couto, Monteiro, Oliveira, Lunet, & Massano, 2014). Following STN DBS, some patients become less depressed while others become more so (Funkiewiez et al., 2004; Couto et al., 2014), with some having suicidal ideations or even committing suicide despite motor improvements (Weintraub et al., 2013; Rodrigues et al., 2010). The reduction of dopaminergic drugs in PD patients receiving DBS might lead to dopamine withdrawal syndrome,

[1] *The patient has taken legal action against the lead neurosurgeon. Legal procedures were still in progress at the time this article was written.*

which could cause depression (Castrioto et al., 2014; Thobois et al., 2010). The ethical concern is how to balance motor improvement with these effects, especially if they seem irreversible.

Our patient experienced depression and eventually attempted suicide, which could have been precipitated by persistent feelings of distress and the breaking down of her relationships with her physicians and ex-husband. The severity of these side effects emphasizes the importance of long-term narrative studies in PD patients receiving DBS in determining how postoperative mood changes affect patients' quality of life, understanding how depressed patients see treatment effects and might feel unsatisfied despite motor improvements, and identifying potential social and environmental factors that could affect postoperative depressive feelings and precipitate suicidal ideations and attempts (Gilbert, 2012; 2013b).

The first-person narrative presented in this study aims to highlight experiences of mania and hypersexuality from a patient's perspective rather than from an external observer's evaluation and to demonstrate the patient's thoughts and feelings when these tendencies and symptoms emerge. These subjective reports are ethically fundamental to making sense of drastic changes that may harm the patient: in particular, negatively affecting what constitutes first-person experiences. By exploring the patient's subjective experience of being implanted, we examine what makes a person who she is: the subject of her own experience—unique and distinct from that of any other subject (Gilbert, 2017). The patient claimed that "I can't be the real me anymore—I can't pretend . . . I think that I felt that the person that I have been [since the intervention] was somehow observing somebody else, but it wasn't me," and "I feel like I am who I am now. But it's not the *me* that went into the surgery that time." These feelings reflect a notion of self-estrangement: in other terms, being the estranged subject of experiences; "estrangement of the self from itself" (Gilbert, 2017). The ethical issue with self-estrangement is that it can be associated with deteriorative aspects (e.g., depressive symptoms) and restorative aspects (e.g., distorted perception of capacities) (Gilbert, Goddard, Viaña et al., 2017). In either case, patients may not cope well with these newly acquired aspects.

The patient's narratives of deteriorative estrangement appear to be compatible with previous literature reporting an increased number of patients perceiving themselves as having an altered or different personal identity following DBS, despite motor improvements. Previous studies have reported patients experiencing feelings of strangeness, including narratives such as the following: "I don't seem to recognize myself without the problems I had before" (Agid et al., 2006) and "I don't recognize myself anymore; I haven't found myself again after the operation" (Schüpbach et al., 2006). Previous studies have highlighted the salient issue that patients suffering from deteriorative self-estrangement were at greater risk of harm, including from suicide attempts (Gilbert, 2015a; 2013a).

Exploring patients' feelings of self-estrangement allows us to comprehend which cognitive, affective, and conative capacities may have been drastically affected, and, as a result, compromise their ability to freely act or make decisions. For instance, our patient reported feeling "more sexual with the surgery than without," leading her to manifest degrees of hypersexuality.[2] The general increase in her sexual arousal and activity, tangential with augmented impulsivity, may call into question whether she is ultimately responsible for some of her behaviors and actions: "I never had felt this lack of power or this giving of power—until I had deep brain stimulation." These first-person experiences have indicated how the patient is aware that her behavior is different from her pre–DBS self and that the hypersexual person post–DBS is questioning who she has become. This is very

[2] *Although reports of increased sexuality immediately after DBS surgery and after initial stimulation (Romito & Albanese, 2010) and of impulsive actions as a result of feelings of grandiosity and energy increase have been presented before (Ugurlu et al., 2014), they have not really highlighted a patient's feelings during these episodes.*

important, because it could assist the medical team in (re)evaluating the harmful outcomes that have occurred despite successfully addressing therapeutic endpoints. For instance, when the psychiatrist recommended that " . . . you need to turn the settings right down to manage it," the patient replied, "Please don't, this is not over the top—this is just joy." These dilemmas echo how a patient might prefer to keep a particular stimulation parameter because of feelings, such as joy, that DBS induces (Chattha, Greene, & Ramdhani, 2015; Krack et al., 2001). However, practitioners' responses to patient requests to operate stimulation at a certain level should always take into account the risk of harm.

As discussed, what characterizes the reported patient's potential postoperative harmful experience, as in other cases (Gilbert, Goddard, Viaña et al., 2017; Agid et al., 2006; Schüpbach et al., 2006), can be understood by way of deteriorative estranged effects. We believe that the patient substantially experienced deteriorative estrangement correlated with a radical and ongoing sense of loss of control over some important capacities, which reflects an involuntary and unintentional shift in her character: to some extent, a "radical disruptive experience which redefines the patient's life" (Gisquet, 2008). These capacities were implicated in her conception of herself as a rational agent, able to decide and freely choose what is in her best interest. Her struggles with postoperative estrangement, especially to reidentify with particular qualitative capacities, through activities, emotions, and aspirations, illustrate a loss of control of some elements of herself. As such, the case report appears to further corroborate the hypothesis that postoperative self-estrangement experiences seem to qualitatively characterize the notion of powerlessness (Gilbert, 2013a), which is often manifested through involuntary self-harming actions or behaviors or loss of control.

The patient went through a spectrum of subjective experiences, articulated in various narratives, from intense distress (suicide attempt) to manifestations of stability (little regret for her previous self). Along the spectrum of feelings associated with self-interpretation of strangeness, the patient reported subjective changes in her capacities. Some of the testimonials show that she initially experienced DBS-induced capacities as not representative or characteristic of herself. This experience of a gap in character has been felt in many cases as a malaise (Gilbert, 2017). In some instances, this malaise took the form of a dispossession of control of some capacities. In this case, such malaise appears to antagonize the patient's ability to appropriate her new capacities. The existence of sudden and persistent capacities that are not embraced by the patient following stimulation is evidence that a different subjective experience of the self has emerged poststimulation. Self-estrangement reflects the idea that feelings of strangeness reach a critical proportion when DBS-induced capacities overpower previous capacities and specific behaviors (Gilbert, 2017). Some aspects of this postoperative overtaking can be negative, as in cases where the patient becomes impulsive. However, not all situations would appear to be negative, as seen with the implanted patient in this case study who enjoyed new sexual capacities and developed artistic ways of expressing herself.

Eventually, the patient managed to come to terms with her newfound self and interests while still being aware that she was no longer her old self. These phenomenological accounts can help the medical team address some issues: in particular, by illustrating variance between the experiences of different subjects, such as affective valence and intensity (Bittlinger, 2017). This could help guide medical decisions to remove, deactivate, or maintain treatment. Understanding nontargeted effects of this therapeutic intervention will better prepare PD patients and physicians for potential side effects of a more interpersonal nature.

Overall, our case illustrates the lack of acknowledgment by this patient's initial medical team concerning the existential dimensions of her postoperative experience. These dimensions translate into three main ethical issues: (1) A patient might prefer not to be implanted with DBS knowing that these changes could occur. However, should the risk be deemed acceptable, then (2) there may be a way to design a better shared decision-making process, involving the patient's family, in order to prepare

everyone for possible identity and personality shifts. Should this process lead to fair negotiation between the patient and his or her family, then (3) all of them must consent to accepting the potential long-term unanticipated harmful consequences (patient: being symptom-free but potentially becoming an unexpected "new" person; family: living with a treated but perhaps unwelcome "new" person). The first issue appears to be a sole and ultimate decision made by the patient that aims to preserve patient sovereignty within his or her entourage. The second issue involves an acceptance of the potential risk, but includes preparatory phases to help the patient and his or her family manage possible unwanted outcomes.[3] The third issue addresses the possibility of adverse outcomes experienced by the patient that are incompatible with her or his family values and expectations. These possible ethical issues reflect the need for patients and families to face existential adversities (including potential psychiatric side effects) that may accompany the alleviation of the patient's motor symptoms.

Conclusions

In this report, we present the narrative of a patient who experienced depression, mania, impulsivity, hypersexuality, and self-estrangement after DBS. Such a narrative can provide support to patients experiencing these unexpected postoperative neuropsychiatric effects, prepare caregivers to deal with potential neuropsychiatric consequences, educate family members about potential sudden behavioral changes, and generate knowledge that could guide prospective patients and their families through the decision-making process leading to implantation. For patients and families, knowing that postoperative neuropsychiatric changes are also experienced by several individuals undergoing DBS treatment could help them understand and appreciate the difficulties caused by these side effects and potentially motivate them to establish or join patient support groups. Finally, this case study illustrates that the perspectives and narratives of patients facing postoperative neuropsychiatric changes and self-estrangement should also be given importance in devising management strategies not only for the motor symptoms of Parkinson's disease but also for the range of non-motor symptoms that are the adverse effects of medication and stimulation.

The narrative approach that we used in describing patient experiences post–DBS sheds an additional light on the procedure's psychiatric effects, demonstrating the need to support patients' postoperative trajectory with a multidisciplinary team. Narrative medicine, especially in psychiatry, facilitates better understanding of patients' experiences, encourages patient participation in illness reporting, and helps align scientific and medical knowledge with specific patient symptoms, needs, and preferences (Holmes, 2000; Schultz & Flasher, 2011). In addition, patient narratives are important tools in informing the public about the disorder by revealing the human side of illnesses (Sachdev, 2011). In this report, the use of a narrative approach sheds light on how feelings of self-estrangement initially caused distress to the patient but eventually led to acceptance and coping. It highlights the importance of not just resolving the motor condition of PD patients but also addressing non-motor symptoms that might arise from treatment. Finally, it makes descriptions of adverse side effects more relatable to future patients and caregivers and gives them a more personal insight on problems and issues, beyond the medical diagnosis of psychiatric conditions, that they might face post–DBS.

As novel implantable brain technologies are developing fast—for instance, in their control by artificial intelligence to target neurological and psychiatric conditions—new ethical issues will likely emerge (Gilbert, Cook, O'Brien, & Illes, 2017;

[3] *Patient postoperative socioenvironmental trajectory is compatible with previous studies reporting postoperative changes associated with family dynamics and restructuring. For instance, "64% of patients who were working before surgery wanted to stop their professional activity, and 65% of those who were married (or lived with a partner) experienced a conjugal crisis after operation" (Agid et al., 2006, p. 410).*

Reardon, 2017; Gilbert, 2015b; Gilbert, Cook, 2015; Gilbert, O'Brien, Cook, 2018). As our case study has demonstrated, keeping in mind the possibility that novel neurotechnologies may have profound existential side effects will be critical for ensuring patients' wellness.

Ethics Approval

This study was conducted in accordance with Tasmanian Human Research Ethics Committee regulations. Patient consent and minimal risk ethics application approval, entitled "H0014820 Deep Brain Stimulation Postoperative Suicidal Ideation within Treatment Resistant Depression: Why Removing the Devices is Not Enough," conform to Tasmanian Human Research Ethics Committee regulations. Ethics approval was obtained in 2015. The patient provided consent to have her narratives included in publications on neuropsychiatric side effects of DBS for PD.

Discussion Questions

1. What obligations do DBS providers and researchers have to offer follow-up care aimed at addressing potential personality and behavior changes that can cause patients distress?

2. What are the trade-offs between the motor benefits of DBS and the potential psychological harm induced by treatments?
Should decision aids be developed to help patients weigh the pros and cons? What would you put into such a decision aid?

3. Should family members have a greater voice in DBS decision-making than in ordinary healthcare decision-making given the potential impact of DBS on personality and behavior?

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VII. Descriptive review of philosophical perspectives on DBS, selfhood, and identity

The literature presented in sections V and VI illustrate possible effects of DBS on preferences, behaviour, personality, self-concept, and socialisation. Some of these reports have been used in the philosophical reflection of how DBS could affect selfhood and identity, with several reflections cited in the publications included in section VI of this chapter (Gilbert et al. 2017; Gilbert & Viaña 2018). These philosophical viewpoints will also be utilised in the discussion on the possible effects of DBS on the selfhood of people with AD in Chapter 6 (Viaña & Gilbert 2018). Considering the word limit for journal publications, the three publications (Gilbert et al. 2017; Gilbert & Viaña 2018; Viaña & Gilbert 2018) citing these philosophical perspectives did not have enough space for a more concrete and extensive description of the views included. As such, this section of Chapter 3 aims to provide readers of this thesis a representative overview of philosophical perspectives on how DBS could influence the selfhood and identity of its recipients. This section neither aims to critically engage with each viewpoint nor argue for a particular position on whether DBS changes identity or not. Rather, its main goal is to introduce to readers who might not have an extensive neurophilosophy background the philosophical discourse on the effects of DBS on selfhood and identity, which would also be used in Chapter 6 (Viaña & Gilbert 2018) to hypothesise how DBS for AD may affect selfhood and its implications on a clinical trial's consent procedure and manner of treating research participants.

In 2009, Walter Glannon highlighted that DBS could alter mental states critical to personality, thought, and behaviour, which could then disrupt the continuity and integrity of psychological properties constituting the self and the experience of persisting through time

as the same person. He suggested that if psychiatric adverse events from DBS such as mania alters the general content, continuity, and integrity of a person's desires, intentions, beliefs, and emotions, then turning on the stimulation seems to turn the PD patient to a different person. Glannon (2009) acknowledged though that for certain PD patients, this alteration in the self that leads to less suffering is preferable to a self with more suffering. In addition, although the manic state would appear to disrupt the thematic unity of the total set of a person's mental states over time and disrupt his or her narrative identity, it does not entail a complete disruption of someone's psychological continuity. There may be enough psychological continuity and narrative integrity for a person to retain a sufficient, albeit weaker, sense of identity to still be the same person that is aware of and can recall what it is like to lose motor control and regain it. Even if there is substantial change, the patient still benefits from the stimulation through relief from motor suffering. As such, potential changes or harms in a person's identity cannot be separated from a comparison of the potential benefit to the patient. Possible psychological and/or psychiatric changes have to be contextualized by the procedure's goal of relieving a patient's suffering.

Schechtman (2010) also posited that DBS-induced psychological and personality changes represent a threat to personal identity and agency. She indicated that both rapid and dramatic relief from symptoms and long-term changes can be alarming or a cause of concern. She cited examples wherein patients and researchers felt terrified by sudden changes in mood caused by stimulation in depressed patients. This can be due to the global nature of the psychological change and to its immediate nature comparable to "flipping a switch", which makes it difficult to attribute the changes as products of the patient's will and effort. Although there is a positive outcome, patients might still see the effect as a threat to identity and

agency. Schechtman (2010) also indicated that long-term changes observed in Parkinson's patients receiving DBS can be perceived as a threat to identity in a way that it leads to problems in patients with adjusting on how to go on with their lives once the motor symptoms of PD have been alleviated. In examining how these changes affect identity, she underscored the use of a narrative perspective, which states that "our selfhood is essentially tied not directly to defining traits, but to our ability to understand ourselves and others in narrative terms" (p. 136, Schechtman 2010). The main idea of this perspective is that as people develop, they see themselves as temporally extended subjects whose past affect their present states and whose current choices and circumstances will likely have implications for the future. Using this narrative perspective, DBS could disrupt a patient's personal narrative through the manner and rapidity of the change, which could break off a current narrative and start a new one. For the long-term changes caused by DBS, disruptions in narrative can be due to the loss of the identity of a person with motor symptoms and difficulties adjusting to a life with relieved symptoms. Despite these potential threats to a person's narrative, DBS can alternatively be seen as something enabling and as a segment of a continuous and self-expressive life narrative when viewed beyond just the period of change and through a longer time bracket. By having a long view of life that allows for instances of radical change to be integrated into an ongoing story, people could find a way to bring DBS into one's narrative rather than to allow it to disrupt it. The threats posed by DBS to personal identity and agency highlight the importance of working with patients pre- and post-operatively to help them construct and maintain a sense of self and agency gracefully despite radical and long-term changes, preventing alienation and ensuring that therapeutic goals are met.

Jotterand and Giordano (2011), defining personal identity as the psychosocial and biological aspects of human development and experience through a body located in time and space, posited that neurostimulation affects certain aspects of personal identity. They highlighted three main issues that must be raised when determining the effect of DBS on personal identity – its effect on neural structures with unforeseeable consequences, the creation of a state of dependence that does not foster a patient's autonomy, and its effect on a patient's rationality or the ability to advance one's ideas and beliefs. They highlighted the importance of evaluating the potential for DBS-induced personality changes, especially on its reversibility upon treatment termination or upon administration of secondary interventions.

Mathews (2011) explored the effect of DBS on personal identity through its effects on a person's sense of oneself as a continuous being over time, with memories and justifications for any changes. Mathews (2011) highlighted the importance of the construct of personal identity in the sense that it influences our views of a person's responsibilities and also our responsibilities towards that individual. She emphasized that DBS might be perceived differently from medication or psychotherapy due to its potential permanence, increased requirement for interaction and dependency on the medical system, and effects that are reversible, reproducible, and immediate, which could result to identity and sense of self changes immediately upon turning the stimulation on. She also raised important questions on the presence of narrative continuity in identity changes and if a patient's and his or her caregiver's views are congruent. She advocated further investigations on evaluating the impact of DBS on personal identity, integrating patients' views of what counts as a risk and benefit. If these changes are evaluated as risks, then new measures and metrics should be

developed to assess them and provide better information on the risks to patients, especially during the stage when patients and their families have to provide informed consent.

Baylis (2013) argued that the claim that DBS threatens personal identity is either false, misdirected, or trivially true. Using a relational perspective on identity, Baylis (2013) posited that the identity of an individual is the negotiated space between how a person sees him or herself as and who other people will allow him to be. She argued that DBS is not and could never be a threat to personal identity since the self is continuously being constituted socially, culturally, and politically. What matters more is how an event or experience is integrated, consciously or unconsciously, into an identity-constituting narrative. She also highlighted the importance of autonomy for it enables people to contribute to the authoring of their lives in a way consistent with their commitments, interests, and values. As such, it is the discriminatory, stigmatizing, and alienating attitude of people towards those with disabilities, rather than DBS, that seriously threatens identity. Finally, she emphasized that if DBS poses as a threat to identity in a way that it limits the way a person views and understands himself, affecting the process of identity formation and subsequent self projection, then any life event or experience is then actually a threat to identity. As such, DBS should not be considered a threat, unless life events are also considered as threats. Although Baylis (2013) argued that DBS is primarily not a threat to identity, she acknowledged that it could potentially threaten agency, especially when brain manipulation results to actions that do not flow from a person's own intentions and beliefs. In this situation, Baylis (2013) posited that DBS may then give rise to a threat to identity.

Klaming and Haselager (2013) suggested that in some patients, DBS may influence mental states that are critical to personality, influencing a patient's unique character traits that are reflected in his or her desires, thought, motivations, and behaviour. In turn, this could affect personal identity, which they defined as the experience of persisting through time as the same person or psychological continuity. By citing the case of a patient with Tourette syndrome who developed an alternate identity state upon increasing the stimulation's amplitude, Klaming and Haselager (2013) presented that DBS can impinge on psychological continuity due to its profound effects on behaviour and memory and influence personal identity to an extent that an alternate personality state can be observed. This case also demonstrates that psychological disruptions induced by DBS can occur relatively quickly due to immediate behavioural changes after stimulation, which also disappear after decreasing the stimulation intensity. As such, DBS can lead to a discontinuity phenomenon regarding character traits, intentions, beliefs, goals, and desires. In addition, even though DBS does not often lead to an alternate identity, severe changes in personality such as having manic and psychotic symptoms could still result in disruptions of psychological continuity, which could also affect a person's mental competence. Finally, they highlighted that although stimulation itself could cause unwanted changes, the sudden discontinuation of stimulation through battery failure could also result in a state prior to treatment that could also be damaging to the patient, such as the occurrence of suicidal thoughts in depressed patients.

Lipsman and Glannon (2013) argued that although DBS is capable of altering fundamental attributes of identity, it is no more of a threat to numerical or narrative identity than any other brain-based process such as advanced dementia or intervention such as brain tumour removal. In this sense, they defined numerical identity as the continuous sense of a

biological self over time independent of experience, whereas narrative identity is made up of memories, details, and experiences that defines who a person is. However, they highlighted that two unique ways in which DBS could influence identity - its ability to be turned off allowing dissociation of the influence of the surgery, implant, and underlying disease process on identity; and in the discrepancy between reported identity change from the perspective of the patient and his or her family. Their second point emphasizes that although patients feel unchanged after the procedure, maintaining a sense of continuity in the experience of self and identity, family members might deem the patient unrecognizable as a result of perceived significant changes in identity. In addition, they highlighted the importance of the degree and consistency of change. A persistent minor negative change that is incongruent to one's general disposition might have a more dramatic influence on one's identity than a temporary major surgery-attributable negative change or than a major positive change that is congruent with the patient's disposition and is a desired effect of the intervention.

Witt et al. (2013) explored the notion of individual identity changes as a result of DBS, which they defined as "deepest values and beliefs which "make someone the person she is" [and] thus involves certain elements or states figuring prominently in a person's mental life" (p. 502, Witt et al. 2013). They presented different models to address whether DBS really leads to changes in identity. The first one is a core-periphery model, which posits that only changes in central attitudes, values, beliefs, ideologies, etc. constitute a substantial change in identity. Another model is the activity model that ascribes a processing of ordering/endorsement or rejection to certain attitudes for them to be central to an individual's identity. Finally, they proposed and pushed for a Foundational Function model wherein certain beliefs are more foundational in which changes in them would entail changes

in countless other beliefs and would result to a discontinuity in the self prior to and after the change. On the other hand, other beliefs are more peripheral, changes in them do not really result to changes in other beliefs and would not have any direct consequences to the identity of a person. They then proposed to use dimensional assessments of personality in order to assess varying levels of changes to identity; however, they posited that current tests might not be adequate to capture changes in individual identity and do not fully cohere with the functional-foundation model that they proposed.

Nyholm and O'Neill (2016) argued that DBS does not exclusively threaten a person's sense of self, and it could sometimes even lead to positive or rehabilitating effects on the patient's self. They explored whether DBS helps bring out the true self, or if it only brings forth superficial aspects of people's selves. They also emphasized the importance of recognizing varying degrees of the effect of DBS on the self. Although radical changes may occur post-stimulation, these radical changes could allow a patient to manifest his or her true self. The effect of DBS on a person's true self is affected by the values or norms that he or she accepts. If a trait that a particular person values is positively influenced by DBS, then that person might achieve a greater self authenticity as a result of DBS. In the context of anorexia nervosa, they argued that DBS might help patients remain in a mindset that fits better with his or her authentic self if the patient had an inclination at some point towards that mindset, even in the absence of DBS, and if the values held by the patient when in an anorexic mindset fall outside of widely-endorsed values by other people.

Overall, philosophical reflection on case reports has led to a wide range of viewpoints on the effect of DBS on selfhood and identity. Some ethicists suggest that it could have an

influence on identity (Klaming & Haselager 2013), leading to changes (Glannon 2009; Mathews 2011) or even posing a threat to it (Schechtman 2010). On the other hand, other neuroethics scholars posit that claims on DBS-associated identity changes are false, misdirected, or trivially true (Baylis 2013), and that any DBS-associated change is no more than a threat to identity than any brain-based process or intervention such as surgery (Lipsman & Glannon 2013). In addition to being cited in the publications (Gilbert et al. 2017; Gilbert & Viaña 2018) included in Section VI of this chapter, some of the points raised by the ethicists in this section will also be applied in examining ethical issues in clinical trials of DBS for AD in Chapters 4, 5, and 6. Whenever these viewpoints are cited in publications incorporated in this thesis, readers could go back to this section to gain more information on the arguments forwarded by different neuroethicists, which hopefully would facilitate better understanding on how they are relevant to points raised in the publications I co-wrote.

Although philosophical reflection is critical in forwarding the academic discourse on DBS-associated sequelae and their effects on selfhood and identity, it is important for philosophers to exercise responsibility in their interpretations of empirical data and always keep in mind the limitations of making conclusions or sweeping statements based on few cases, considering that hundreds of thousands of people have received DBS. To conclude this chapter, the article of Gilbert, Viaña and Ineichen (2018) will be presented to highlight the possibility that bioethical discussions could lead to an ethics bubble, which could have an effect on participant decisions. By illustrating that despite numerous neuroethical claims that DBS could affect personality, identity, agency, authenticity, autonomy, and self (PIAAAS), only few systematic empirical studies have been conducted to determine the actual effect of DBS in at least one of these domains. More so, most of the empirical studies did not directly

attribute social adjustment difficulties of patients to DBS, but rather to difficulties in re-integrating to their familial and social environment. Overall, we emphasize that although philosophical dissection of DBS-associated phenomenon can contribute to the acknowledgement of its risks and effects on individuals and society, grounding it in medical realities would ensure the accuracy of the claims presented and properly inform prospective patients or trial participants of the potential risks and benefits of DBS. Given that I am a co-author of this paper, it is included in this section and can be found in pages 110 to 126.

Considering that exaggerated claims can result from the overinterpretation and non-systematic analysis of cited empirical studies, it is important to acknowledge the limitations of qualitative empirical studies themselves that could also contribute to hyperinflated pronouncements. One of which is the possibility of bias in terms of the segment of the interview included in the paper, manifested as “cherry picking” of data presented in order to conform with a particular pre-established conceptual stance, hypothesis, or agenda of the researchers (Morse 2015; Galdas 2017). In addition, there could also be bias in the selection of the interviewees and in the formulation of questions, especially in the comparison of different interventions in samples that are likewise inherently non-equivalent. Though certain steps such as member checks and triangulation can be taken to lessen bias (Morse 2015), it is always important for qualitive researchers and those who cite their work to acknowledge inherent limitations of qualitative research in order to moderate the extent of any claims and conclusions.

Our article on the potential ethics bubble on the effects of DBS on PIAAAS (Gilbert, Viaña & Ineichen 2018) has encouraged deeper reflection on how my and my collaborators’

previous conceptual and empirical works could have likewise contributed to an ethics bubble, and on how future work conducting empirical research or drawing from results of qualitative studies could be improved so as not to create an impenetrable bubble that distorts accurate perception of actual risks and potential benefits of a certain technology or intervention. One evidence of such reflection is the citation of Frederic Gilbert's (2013, 2015) previous works on how DBS in people with treatment-resistant depression could lead to self-estrangement. In the article of Gilbert, Viaña and Ineichen (2018), the papers of Gilbert (2013, 2015) were included in Table 2 as examples of philosophical explanations about the putative impact of DBS on PIAAAS. Including Gilbert's (2013, 2015) papers as possible contributors to the PIAAAS bubble is evidence of growing self-awareness and an increase in critical perspective during research and publication, in line with pragmatism's (Fins, Bacchetta & Miller 1997) emphasis on periodic review and in modifying previously proposed courses of action as research evolves. The critical appraisal of one's previous work is also a demonstration of commitment to moderate fallibilism and epistemological humility advocated by pragmatism (Arras 2002), acknowledging how one's previous views could have contributed to an ethics bubble and how this could be corrected. The use of the term "we neuroethicists" or "we, the neuroethicists" in the paper also exemplifies that the goal of the article of Gilbert, Viaña and Ineichen (2018) is not to simply delegate blame to other ethicists for generating hype on the extended effects of DBS, but also to critically appraise one's previous work and the way it has also contributed to the generation of a speculative bubble. Finally, in order to achieve a full pragmatic approach (Fins, Bacchetta & Miler 1997; Racine 2008b) in addressing the issue of ethics hype on the effects of DBS on PIAAAS, it is important to facilitate deliberation with patients, physicians, and ethicists on how they perceive philosophical reflections on DBS's effects on PIAAAS could affect patient willingness to undergo DBS and physician decision to offer it as a

potential therapy. This deliberation would allow testing of the practical usefulness and applicability of the recommendations forwarded by Gilbert, Viaña, and Ineichen (2018) and also espouse mutual trust and respect among various stakeholders (Tong 1997) in the applications of DBS to movement disorders and in its expanding therapeutic applications.

Although Gilbert, Viaña, and Ineichen (2018) caution against unwarranted and unsubstantiated speculation on the effects of DBS on PIAAAS, we do not aim to disregard the role and importance of speculation. Speculation in bioethics involves an attempt to predict scenarios and draw conclusions on their possible outcomes based on assumptions that cannot be verified by present empirical or scientific claims. We acknowledge that through this effort, major ethical challenges can be foreseen before a novel technology or a new application of an existing technology is introduced and disseminated (Racine et al. 2014), allowing adequate steps to be taken to avert or deal with these challenges (Roache 2008). Furthermore, we agree with Roache (2008) that properly grounded and knowledge-based speculation (Racine et al. 2014) encourages ethical evaluation at the start or early stages of a project, helping avoid unethical or ethically misguided scientific endeavours before a significant amount of money, time, and careers has been invested in them. Speculation, even of future scenarios with low probabilities of occurring, could also be instrumental in motivating the conduct of crucial ethical projects (Roache 2008) that address present issues.

Pragmatism's commitment to fallibilism (Arras 2002), acknowledging that knowledge is not absolute (Brown 2008), also signifies room for making speculations, as long as they follow a thorough review of empirical information (Fins, Bacchetta & Miller 1997; Fins 2005) and discuss the limitations of various methods in obtaining such information, as indicated in

the paper of Gilbert, Viaña, and Ineichen (2018) and in one of the preceding paragraphs. With pragmatism's emphasis on scenario and context-based ethical deliberation (Fins, Bacchetta & Miler 1997; Racine 2008b), it is important to critically appraise previous speculations and conclusions made to see how well they still fit within a particular context and the extent of the applicability of any claims made. For instance, the article of Gilbert, Viaña, and Ineichen (2018) highlighted that "the prevalence and incidence of effects on PIAAAS might not be exclusively correlated with a specific DBS target and/or stimulation parameter. It should rather be seen as a result of the interaction between electrical stimulation, adjustments in medication, and natural progression of the disease" (p. 10, Gilbert, Viaña & Ineichen 2018). This claim underscores the significance of context in translating ethical claims. In addition to taking into account biological details of a case, it is essential to factor in family dynamics, institutional arrangements, social norms (Fins, Bacchetta & Miller 1997), cultural practices, and broader environmental factors that could affect the extent in which a person receiving DBS adjusts and adapts to DBS therapy. The applicability, importance, and relevance of any speculations made should be viewed from both techno-scientific and psycho-socio-environmental vantage points, considering not just the perspectives of people receiving DBS but also of the attending medical professionals and of family and caregivers. Finally, fallibilism should be applied to both qualitative and quantitative claims. Potential biases due to conflicts of interest (Bebbington 2003) and/or limitations and challenges in gathering comprehensive quantitative information (Fairchild et al. 2018) should be acknowledged when presenting and drawing claims from quantitative data. For instance, the applicability to ethical claims of prevalence rates of various psychiatric symptoms in people with Parkinson's disease indicated in the paper of Gilbert, Viaña, and Ineichen (2018) might be affected by location, time period, specific patient population, institutional capacities, and other socio-environmental factors

that influence the reporting and diagnosis of psychiatric symptoms (Woodall et al. 2010; Kohrt et al. 2014).

In the three main publications presented in Chapters 4, 5, and 6, caution was exercised in the claims made to ensure that those that are hypothetical are clearly indicated as such. Although most of the ideas and concerns raised are based on empirical studies on DBS for AD or other indications, or in fornix DBS in animal models, it is important to acknowledge that there are currently no extensive qualitative studies on the effects of DBS on personality, identity, selfhood, and social adjustment in people with AD, similar to what Houeto et al. (2002), Agid et al. (2006), and Gilbert et al. (2017) performed. As such, the best that can be done to reflect on these possible effects is to review studies on DBS in other indications and/or for other brain regions, while emphasizing that these may or may not happen in DBS for AD given the difference in pathophysiology, brain regions targeted, social attitudes towards AD, and lived experiences of people with AD. Furthermore, in order to apply a complete pragmatic approach (Fins, Bacchetta & Miler 1997; Racine 2008b) to investigating and understanding the ethical concerns associated with DBS for AD, deliberation with patients, family members and caregivers, researchers, and medical staff should be made using recommendations in this paper's three main publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) as guiding frameworks. This would ensure that ethical recommendations are actually enacted and evaluated, in addition to determining additional techno-scientific and psycho-socio-environmental factors, especially participant and caregiver actual lived experiences, that are crucial in developing more sound and adaptive recommendations for ongoing and future DBS for AD clinical trials.

The following paper has John Noel M. Viaña as a co-author and thus, is included in this doctoral dissertation:

Pages 110 to 126:

Gilbert, F, **Viaña, JNM** & Ineichen, C. Copyright 2018, 'Deflating the "DBS causes personality changes" bubble', Originally published in *Neuroethics* and reprinted by permission from *Springer Nature B.V. (Netherlands)*. Article online, published first on June 19, 2018. doi: 10.1007/s12152-018-9373-8. Available from: https://link.springer.com/article/10.1007%2Fs12152-018-9373-8

Note: On page 111, there is a period after "has the potential to alter essential features of a patient's personhood, including mood, personality, and cognitive abilities [7]". This was a typographical error, and the period should not have been there. "[7]., etc." should be replaced with "[7], etc." I would like to thank one of the examiners for pointing out this mistake.

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ORIGINAL PAPER

Deflating the "DBS causes personality changes" bubble

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Abstract The idea that deep brain stimulation (DBS) induces changes to personality, identity, agency, authenticity, autonomy and self (PIAAAS) is so deeply entrenched within neuroethics discourses that it has become an unchallenged narrative. In this article, we critically assess evidence about putative effects of DBS on PIAAAS. We conducted a literature review of more than 1535 articles to investigate the prevalence of scientific evidence regarding these potential DBS-induced changes. While we observed an increase in the number of publications in theoretical neuroethics that mention putative DBS-induced changes to patients' postoperative PIAAAS, we found a critical lack of primary empirical studies corroborating these claims. Our findings strongly suggest that the theoretical neuroethics debate on putative effects of DBS relies on very limited empirical evidence and is, instead, reliant on unsubstantiated speculative assumptions probably *in lieu* of robust evidence. As such, this may reflect the likelihood of a speculative neuroethics bubble that may need to be deflated. Nevertheless, despite the low number of first-hand primary studies and large number of marginal and single case reports, potential postoperative DBS changes experienced by patients remain a critical ethical concern. We recommend further empirical research in order to enhance theoretical neuroethics work in the area. In particular, we call for the development of better instruments capable of capturing potential postoperative variations of PIAAAS.

Keywords Adverse effects · Autonomy · Agency · Assumption · Authenticity · Control group · Deep brain stimulation · Evidence · Identity · Neuroethics · Personality · Self

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Introduction

In theoretical neuroethics, the idea that "personality changes and possible loss of personal identity can follow from the introduction of foreign (biological or technical) material into the brain" [1] is pervasive and highly recurrent. In particular, deep brain stimulation (DBS) has been commonly associated with such alleged changes, and consequently, it has been a central concern in theoretical neuroethics. Many publications suggest that when "DBS is applied to enhancing or maintaining movement, the specter of Phineas Gage, whose personality changed so radically after his brain was pierced by a tamping iron, haunts us. [DBS] may fundamentally alter selves" [2].

Suggestions that DBS may induce personality changes are strongly established within theoretical neuroethics narratives, and they are articulated in many ways. For instance, Schechtman declares that "personality changes [following DBS] represent a threat to personal identity

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and agency" [3]. Witt and colleagues assert that "the risk of becoming another person following [DBS] surgery is alarming" [4]. Others argue that DBS "pose[s] manifold medical, philosophical and ethical questions as regards the personality, personal identity, individual responsibility, autonomy, authenticity and self-perception of the person involved" [5]; or that DBS "may alter a range of mental states critical to thought, personality and behaviour … disrupt[ing] the integrity and continuity of the psychological properties that constitute the self and one's experience of persisting through time as the same person" [6]; or that DBS "has the potential to alter essential features of a patient's personhood, including mood, personality, and cognitive abilities" [7]., etc. These examples are a fraction of many claims frequently published in neuroethics articles about the alleged adverse effects of DBS. In fact, since the publication of Schüpbach et al.'s seminal work in [8], entitled "Neurosurgery in Parkinson's disease: A distressed mind in a repaired body?" [8], there has been a substantial increase in theoretical neuroethics articles exploring the putative impacts of DBS on personality, identity, agency, autonomy, authenticity, and self (PIAAAS). The idea that DBS induces PIAAAS changes is so deeply entrenched within neuroethics discourses that it has become an unchallenged narrative. However, it comes with some surprise that this narrative has not been rigorously scrutinized. To our knowledge, few studies investigate the occurrence and type of empirical evidence demonstrating putative effects of DBS on PIAAAS.

The purpose of this study is to address this issue. We critically examine and assess empirical evidence about the putative effects of DBS on patients' PIAAAS. In particular, our main objective is to identify evidence within the neuroscientific and medical literature substantiating the conclusion that DBS causes PIAAAS changes, which appears to be persistently suggested in the theoretical neuroethics narrative. Accordingly, this paper targets substantial and consequential effects impacting patients' PIAAAS, primarily considering deteriorative and estrangement-inducing adverse effects of DBS [9]. Our second objective is to examine the prevalence of articles discussing the alleged effects of DBS on patients' PIAAAS in the theoretical neuroethics literature. Our third goal is to assess our findings, especially, whether the theoretical neuroethics literature is engaged in a speculative bubble, which may need to be deflated and rectified by grounding it in empirical evidence as available through the scholarly neuroscientific and medical literature.

Methods

To identify and examine the prevalence of articles discussing putative effects of DBS on patients' personality, identity, agency, authenticity, autonomy, and self (PIAAAS), we searched the archives of some leading 30 bioethics journals[1] and AJOB Neuroscience, as well as relevant articles indexed in ProjectMuse, JSTOR, PhilPapers, and PhilIndex (limiting our search to academic journals). Furthermore, we examined the prevalence of empirical evidence supporting links between DBS and PIAAAS explicitly. To this purpose, we searched for relevant articles in the databases of PubMed, Scopus, Embase, Web of Science, PsycAarticles, Psychology & Behavioral Sciences Collection (PBSC), PsycInfo (via Ovid), and Psychiatry Online (excluding news articles). Articles until May 2017 were considered.

Articles were retrieved using the search terms "*deep brain stimulation*" *AND (personality OR identity OR autonomy OR agency OR authenticity OR self).* Duplicate articles were removed manually with the help of EndNote's "Find duplicates" function. To determine whether articles were mainly discussing DBS, we used the web browser's (Google Chrome) or Adobe Reader's search function to get an overview of the extent to which the term DBS appeared in each article under review. Articles that did not mention DBS in the abstract or did not dedicate at least half of the text to discussing DBS were excluded. The remaining articles—those that involved 'substantial' discussion of DBS—were then individually examined to determine the number of times any element of PIAAAS was mentioned as determined through a search for *(personality OR identity OR autonomy OR agency OR authenticity OR self)* using the browser or Adobe Reader's Search function. The number of mentions for each search component were then tabulated in an Excel sheet. Articles that did not mention at all any component of PIAAAS were automatically excluded. The abstract and/or actual text of articles that mentioned any of these terms were examined further to see if they really explored the effect of DBS on PIAAAS or if these terms were just mentioned in passing. In some

[1] Please refer to Annex 1 to see the full list of journals.

cases, bioethics articles might make over 100 mentions of the terms PIAAAS (taken collectively), while scientific articles might make as little as five (or fewer) of the same mentions (taken collectively).

Articles reporting primary studies or case studies were identified and examined manually. We defined primary studies as new reports of clinical cases involving first-hand interviews or clinical studies involving implanted patients. In other words, a first-hand primary study is a new clinical report involving at least one patient undergoing psychometric tests or being consulted in a clinical setting or being interviewed for the purpose of examining potential DBS-induced PIAAAS. Our final inclusion and exclusion criteria were based on the evaluation of the primary study's core text and explicit conclusion. Articles with primary data were identified as first-hand literature; consequently, articles that did not directly gather PIAAAS-relevant data from patients were not considered as valid first-hand evidence. Articles not reporting novel empirical evidence but that still discuss already published primary empirical studies in relation to PIAAAS were manually identified as second-hand literature. Articles that discuss PIAAAS but not referring to any primary research (of a kind that reported new empirical evidence) were manually identified as third-hand literature.

Results

In General

A total of 1535 articles were assessed. We found 64 articles that qualified as first-hand studies (See Fig. 1 "Primary Study Articles"[2]). However, after assessing these articles one by one, we found that 67% ($n = 43$) do not support direct links of DBS on PIAAAS. Analysis of the remaining 21 articles revealed that 13 articles were marginal or single case studies.[3] As a result, only 8 studies qualified as significant evidence (12.5% of 64 primary research), involving 168 patients in total (see Table 1: First Hand Primary Research).[4] It is crucial to note that none of these 8 studies had control groups. Generally, it can be more difficult to evaluate the outcome and attribute the cause of the observed effect when a control group is lacking. Prospective, randomized, and sham-controlled trials, for example, represent particularly neat study designs to investigate effects of DBS. Strikingly, when a control group was included as part of the experimental procedure, for example in Schüpbach et al. [18], the control group, which did not receive stimulation, experienced more severe adverse effects related to PIAAAS than the actual group that received stimulation.

We observed a contrast between the number of publications in theoretical neuroethics and the number of published primary research articles (see Fig. 2). A substantial increase in publication in theoretical neuroethics appears to occur starting in 2009.

In Particular

1) Conclusions of studies not matching neuroethics claims

When assessing the strength of evidence referred to in the theoretical neuroethics literature, we observed that the most cited articles in Table 1[5] are three seminal manuscripts published by Schüpbach et al. [8], Agid et al. [11] and Houeto et al. [10]. Interestingly, the articles by Schüpbach et al. [8] and Agid et al. [11] are two distinct versions of the same French trial study, based on the same interviews, involving the same 29

[2] Primary study articles explicitly naming PIAAAS in their published work.

[3] By marginal reports, we understand case reports not well detailed. Marginal reports mention some events in articles, nothing more. For instance, most articles marginally report "out of 27 patients implanted, 1 patient experienced hyper-sexuality following surgery" without providing more details. From marginal reports, it is difficult to derive causation, in particular also impossible to exclude co-variables. Hence, by marginal reports we include anecdotal reports, single-patient case reports.

[4] Involving 168 patients in total, but not all 168 patients' experiences would qualify as evidence for a link between DBS and PIAAAS changes. Even if marginal and case reports were included in our final total, it would not significantly change the prevalence (see our Discussion). To our knowledge, the most cited case report in neuroethics is the one by Leentjens et al. [17]. Unfortunately, most marginal and case reports in the literature are not like Leentjens et al. [17]. The report of Leentjens et al. is a unique example where clinicians were turning off/on the stimulation and were able to directly and instantaneously observe behavioral changes occurring (accordingly, they were capable of excluding some variables as contributing to these changes). But if we include the Leentjens et al.'s single case report in our final count, we have to include all the marginal case reports. Most marginal reports strictly mention events in articles, without providing much details or excluding co-variables. Including marginal case reports would be including occurrences where essential details about the cause of the observed changes are missing.

[5] As reported by Google Scholar citation metrics

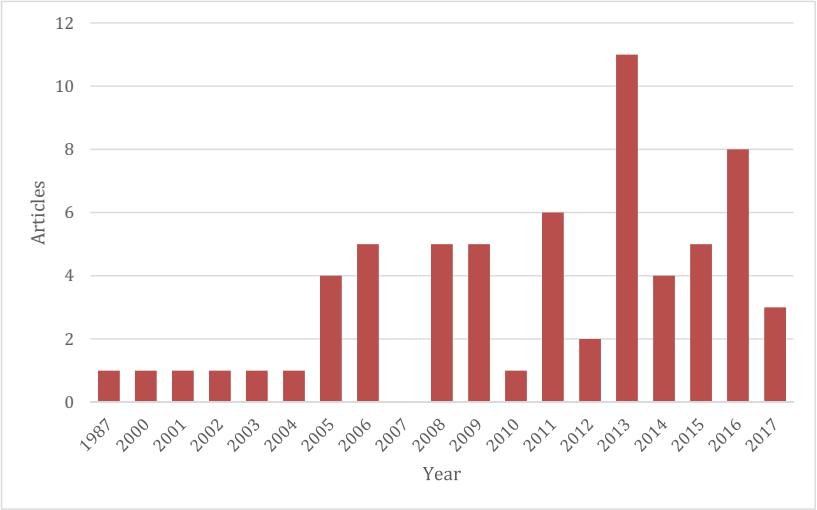

Fig. 1 Number of primary articles on the putative effects of DBS on patient PIAAAS until May 2017

patients. Despite being referenced, cited, and discussed in theoretical neuroethics as empirical evidence demonstrating the effects of DBS on PIAAAS, both articles do not support this conclusion. Agid et al. [11] concluded:

> It seems more likely that the difficulty in social integration experienced by our operated patients resulted, not directly from a modification of the patients' personality, but rather indirectly from a difficulty of reintegrating into the socio-familial and professional environment [11].

At the same time, Schüpbach et al. [8] concluded:

> it was shown that [DBS] led to an overall improvement in mood, anxiety, and quality of life. Now, in spite of the excellent motor outcome, it is clear that the operation can result in poor adjustment of the patient to his or her personal, family, and socio-professional life. Whether this is a purely reactive response to a new situation or whether it is caused by an effect of STN stimulation on behavior, or both, remains to be elucidated. [8]

An article published later by Schüpbach et al. [18] that included a group of people with Parkinson's disease (PD) treated with DBS and a matched control group not treated with DBS (both groups with a follow-up period of 2 years), found that the control group experienced a higher rate of psychiatric adverse effects related to PIAAAS compared to the group treated with DBS.

On their side, Houeto et al. [10] reported 8 patients (out of 24) who experienced changes related to PIAAAS following DBS implantation, but they observed that postoperative "psychiatric disorders consisted of amplification or decompensation of previously existing disorders that had sometimes passed unnoticed" before implantation [10]. In other words, DBS did not initiate the onset of postoperative psychiatric disorders; rather, patients were already suffering from these disorders prior to implantation. Put simply, Parkinson's disease symptoms may have 'masked' psychiatric symptoms; DBS helped keep Parkinson's disease symptoms under control, with the decompensation and manifestation of psychiatric symptoms as an unintended adverse effect.

2) Conceptual discussions based on few quotes.

Given the scarce evidence, as reported above, many neuroethicists and philosophers selected specific quotes from "Schüpbach et al. [8]" or "Agid et al. [11]" to introduce, support, and illustrate their philosophical approach regarding the link of DBS to changes of implanted patients' PIAAAS. One of the most fascinating quotes used by conceptual neuroethicists is the reported experience of an implanted female French patient who declared after surgery: "I feel like an electric doll" [8]. Surprisingly, we found that this specific quote was not accurately translated in Agid et al. [11], where the patients' statement appeared as: "I'm an electric doll" [11]. We would like to highlight the importance of these semantic points because establishing a philosophical theory on a few selective quotes, particularly when words such as "I feel" or "I am" largely differ in their meaning, does not represent robust evidence.

Table 1 First hand primary research

Author(s)	Type of Patients	Title	Numbers of patients	Conclusion
Houeto et al. [10]	PD	Behavioural disorders, Parkinson's disease and subthalamic stimulation	24	8 out 24 patients displayed postoperative changes; however, the authors advanced that postoperative "psychiatric disorders consisted of amplification or decompensation of previously existing disorders". In other terms, PD symptoms were inhibiting psychiatric disorders, but with stimulation keeping symptoms under control, some pre-existing psychiatric disorders were manifested.
Agid et al. [11]	PD	Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so?	29	"It seems more likely that the difficulty in social integration experienced by our operated patients resulted, not directly from a modification of the patients' personality, but rather indirectly from a difficulty of reintegrating into the socio-familial and professional environment"
Schüpbach et al. [8]	PD	Neurosurgery in Parkinson disease: A distressed mind in a repaired body?	29 (same patients as Agid et al. [11])*	"It was shown that neurosurgery led to an overall improvement in mood, anxiety, and quality of life. Now, in spite of the excellent motor outcome, it is clear that the operation can result in poor *adjustment* of the patient to his or her personal, family, and socio-professional life. Whether this is a purely reactive response to a new situation or whether it is caused by an effect of STN stimulation on behavior, or both, remains to be elucidated."
Gisquet [12]	PD	Cerebral implants and Parkinson's disease: a unique form of biographical disruption?	30	"DBS suppresses the most striking symptoms of Parkinson's disease, but at the same time the patient loses control over managing the illness and experiences significant changes in personality. Cerebral implants are a unique form of biographical disruption of which neither physicians nor patients measure the impact."
de Haan et al. [13]	OCD	The phenomenology of Deep Brain Stimulation-induced changes in Obsessive-Compulsive Disorder patients: An enactive affordance-based model	14	No direct conclusion in relation to PIAAAS.
de Haan et al. [14]	OCD	Effects of Deep Brain Stimulation on the lived experience of Obsessive-Compulsive Disorder patients	18 (14 are the same patients from de Haan 2013).	"Apart from the previously documented improvement of mood, diminishment of anxiety, and increase of impulsivity, we also found changes such as an increase in trust, self-reliance, and self-confidence, a more unreflective mode of engagement, and a more careless stance on things."
Lewis et al. [15]	PD	Subjectively perceived personality and mood changes associated with subthalamic stimulation in patients with Parkinson's disease	27	"Personality changes were perceived by six of 27 (22%) patients and by 10 of 23 caregivers (44%). […] Our results show that a high proportion of PD patients and caregivers perceived personality changes under STN-DBS, emphasizing the relevance of this topic. Mood changed in positive and negative directions. Standard measurement scales failed to adequately reflect personality or mood changes subjectively perceived by patients."
Pham et al. [16]	PD	Personality Changes after Deep Brain Stimulation in Parkinson's Disease	40	"STN-DBS in PD patients is associated with personality changes in the direction of increased impulsivity". Impulsivity changes were mostly perceived by relatives not patients after 3 months of stimulation.

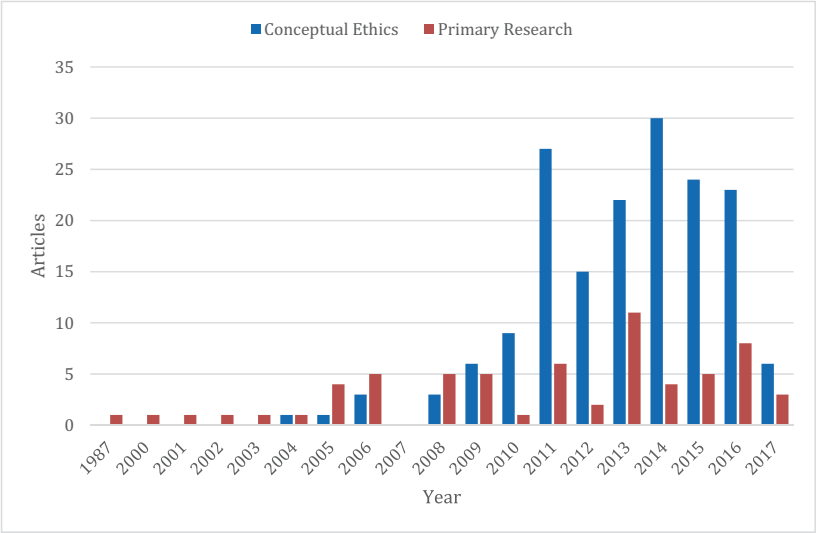

Fig. 2 Theoretical neuroethics and primary research articles on the putative effects of DBS on patients' PIAAAS until May 2017

This highlight the importance of not just basing theroetical arguments on some selective quotes. In addition, one would think that such nuances do make a differences in the theroetical discourse, even though, the error for disseminating a wrong translation was not on the part of neuroethicists, in this case. However, such a discrepancy in translation suggests that we (neuroethicists) should look more carefully from where these quotes are taken from and how they are being used (purportedly) as evidence within our work. Ontologically speaking, one could strongly question and dispute a philosophical conclusion based on the sentence "I feel like an electric doll", as it might not entail the same philosophical view as the quote, "I'm an electric doll" (while the latter quote may involve a psychotic (delusional) episode, the former could simply represent a playful and moody remark). Importantly, this also means that professional interviewers have a duty to try identifying what the interviewees mean when verbalizing such statements, and more importantly, translations should be identical across different publications and should faithfully capture the verbal expressions voiced by patients, along with providing a description of the context in which these expressions were made. As well, this highlights that philosophers quoting these first-hand studies may need to provide more than just fragments of the quote, preferably include a longer tract of quoted text that better reveals the patients intended meaning, and mention the context as well, especially if this was reported or described in the primary study.

3) Postoperative outcomes related to pathology rather than technology

As indicated in Houeto et al.'s conclusion [10], a neurodegenerative disease such a Parkinson's disease may entail psychiatric symptoms due to advancement of the degenerative process, a phenomenon that does not necessarily translate to other diseases, such as dystonia. Based on (still scarce) qualitative research outcomes, it could be suggested that postoperative adverse effects on PIAAAS are more related to disease progression rather than to DBS itself. For instance, interviews conducted by Hariz et al. [19], capturing subjective experiences of 30 patients implanted with DBS for treating their dystonia, reveal that, overall, patients felt they "still [were] the same person inside, but with new abilities and another physical appearance, [which] was difficult to comprehend and come to terms with". [12] As an example, Hariz et al. [19] quoted a patient reporting: "Now, even though I have been given a new body I haven't been given a new mind. It's like plastic surgery, you might change your nose but how you feel about yourself is still the same" [19]. Elsewhere, de Haan et al. [14], after interviewing 18 OCD patients implanted with DBS, concluded that: "Apart from the previously documented improvement of mood, diminishment of anxiety, and increase of impulsivity, we also found changes such as an increase in trust, self-reliance, and self-confidence, a more unreflective mode of engagement, and a more careless stance on things" [14]. Our review found that when the putative effects of DBS on

PIAAAS are raised by theoretical neuroethicists, most authors do not distinguish diseases and stimulation parameters —most generalize their conclusions concerning the putative effects of DBS on PIAAAS of patients being treated for Parkinson's disease to how they understand the effects of DBS on PIAAS for patients with other conditions and potentially, with leads implanted in other brain regions or with different stimulation parameters. The presumption here is that all patients suffering from different presenting neurological conditions and stimulated in different brain regions and with differing parameters would react in the exact same way to treatment. For example, Nyholm and O'Neill [20] in their conceptual study about the effects of DBS on treatment-refractory anorexia nervosa individuals selected cases from different patients implanted with DBS targeting distinct pathologies: for instance, Parkinson's and OCD. Our findings show that there is no evidence pointing toward an identical treatment reaction for DBS targeting different neurological conditions. Although we do not say that unintended effects of DBS can be excluded per se, we aim to highlight that theoretical neuroethics publications should always acknowledge that DBS is not a monolithic technology and that the region and parameters of stimulation interact with the pathophysiology of the disorder, all of which contribute to the overall effect of the surgery and stimulation.

4) Assumptions

We discovered some commonly accepted assumptions among conceptual neuroethicists and philosophers, particularly in third-hand literature. Assumptions include claims without any corroborating empirical evidence. In those cases, manuscripts discuss putative impacts of DBS on PIAAAS without referring to first-hand primary research. For instance, in order to support the hypothesis that implantable devices are a philosophical and ethical problem, Schermer [21] quotes Hasson's view that brain implants may be a "reason to reconsider our criteria for personal identity and personality changes" [1]. It is essential to note that Hasson's conceptual paper does not refer at all to any first-hand primary research. Elsewhere, Johansson et al. advance the claim that, "[p]otential alterations of personality seem […] to be relevant for most DBS indications" [22]. It is important to note that these same authors, in other important works, refer to first-hand primary research [23, 24]. However, these examples of unsubstantiated claims—i.e. claims lacking any reference to primary research—as appearing in third-hand literature illustrate a trend across the theoretical neuroethics literature where authors rely on rare empirical evidence to argue their case, as statements based on lack of evidence go unchallenged. It goes without saying that purely theoretic work is warranted and highly valuable. Neuroethicists have more than the freedom to reflect on PIAAAS, but it is potentially misleading if they either bring it in connection with empirical findings that do not corroborate their claims.

To the best of our knowledge, the assumption that DBS alters PIAAAS first appears to have been explicitly articulated in a scholarly publication with the work of Gisquet [12]. Gisquet, interviewing patients implanted with DBS, declared that her study was "based on the assumption that a treatment using biotechnical techniques is a unique disruptive experience which redefines the patient's life" [12]. Incidentally, from the moment the assumption was formulated and published in the literature in 2009 (see Fig. 2), across all publications in neuroethics, the prevalence of theoretical manuscripts increased, while studies reporting empirical evidence diminished overall. Although speculation in ethics can be a very valuable tool [25], the lack of empirical evidence showing that DBS induces PIAAAS changes is concerning and reflects a potential speculative ethics bubble, which might need to be deflated.

Discussion

In general, we found that the discussion about putative effects of DBS on patients' PIAAAS in theoretical debates is supported by only a small sample of empirical evidence, which strongly suggests that this discussion relies on a limited amount of facts rather than on substantial empirical evidence. Theoretical neuroethics in the context of DBS-related discussions about PIAAAS is mostly reliant upon second-hand and third-hand literature.

There is considerable diversity in the way putative effects of DBS on patients' postoperative life have been described in the literature, particularly in theoretical neuroethics (see Table 2: Sample of philosophical explanations about putative impact of DBS on PIAAAS). These descriptions seem to serve the authors' philosophical accounts rather than reflect first-hand primary study conclusions. For instance, according to Kraemer [33], "by employing the philosophical framework of authenticity and alienation, we are led to call into question the psychological assessment of the three case studies of Parkinson patients who underwent changes in their personalities and preferences after successful treatment with DBS". To support her claims, she refers to Schüpbach et al. [8]. However, as indicated above, Schüpbach et al. [8] do not conclude that patients' personalities were impacted by DBS.[6] Elsewhere, Witt et al. [4] assert "we will begin our discussion with a few quotes from a case reported by Schüpbach et al. It will give us an impression of what proponents of the Change-of-Identify Thesis presumably have in mind when ascertaining 'alterations in the patient's identity". Here too, there seems to be a misinterpretation of the findings of Schüpbach et al., who do not conclude anything about how DBS impacts patient identity.[7] In a very influential paper (citation count 90 with Google Scholar at the time of writing), Baylis affirms:

> "DBS is such a threat but only insofar as it is a threat to agency—the ability to make informed and rational choices—as when a person's actions do not flow from her intentions or beliefs but rather are the result of direct brain manipulation. Here it is worth noting that following DBS patients not only report "I don't feel like myself anymore," and "I haven't found myself again after the operation," they also report "I feel like a robot," and "I feel like an electric doll ".

To support this philosophical claim, she refers to Schüpbach et al. [8]. However, Schüpbach et al.'s [8] article explicitly states that these quotes: "I feel like a robot," and "I feel like an electric doll" are given in the context of discussions of "altered body image", not agency. For instance, Schüpbach et al.'s [8] manuscript states: "1) Altered body image: Only 6 patients (20%) thought about the implanted material in terms of body image and formed a mental representation of the stimulator and the electrodes." Schüpbach et al.'s [8] do not suggest anything about how DBS might alter patients' deliberation, decision-making or agency. Our goal here is not to single out each relevant claim made in the philosophical and theoretical neuroethics literature and to check whether it is supported by empirical evidence. After all, part of the important mission of philosophy and theoretical neuroethics, as seen in the great conceptual work of Baylis and others cited above, is to speculate about concepts and to indulge in thoughtful enquiry, not necessarily trying to ground them in empirical facts. Instead, our goal is to stress that Table 2 represents a sample of some of the philosophical speculations about the putative impacts of DBS on PIAAAS, which appear not to accurately reflect the conclusions made by the first-hand primary studies.

Out of 64 first-hand primary studies, 43 did not corroborate evidence that DBS leads to PIAAAS alteration. Out of the remaining 21 articles, 13 were marginal or single reports. By virtue of the fact that marginal or single observations do not constitute robust data leading to definitive scientific conclusions, our study indicates that the theoretical neuroethics literature may rely on unsubstantiated speculative assumptions *in lieu* of robust evidence. Marginal or single findings are discounted because they are mostly reported without any objective measurement and may not include extensive medical information, which make these studies difficult to replicate and compare with other studies. In addition, they do not provide the actual incidence of DBS-induced PIAAAS in a particular cohort of individuals that received DBS for a particular disorder in that institution. In general, to establish cause-and-effect relationships, study subjects, for example, can be divided into experimental and control groups. Therefore, double blind randomized controlled trials (RCT's) are considered one form of study design (besides e.g. longitudinal and time series studies) for establishing such relationships [40]. In RCT's, differences in outcomes are attributable to different treatments received in such between-group designs because the distribution of confounders is balanced across experimental conditions by design [41]. In comparison to control-group designs, case-studies are often characterized by poor internal validity due to the fact that there is nothing to compare the result to. As a final addition, in principle, studies and reviews investigating

[6] Not only Schüpbach et al. do not conclude this, they exclude personalities as an explanation in their Agid et al. [11] version. See our section "Conclusions of studies not matching neuroethics claims".

[7] In addition, the concept of identity is not alluded to nor is used once in this published study.

Table 2 Sample of philosophical explanation about DBS putative impact on PIAAAS

Discussed by	DBS impacts characterised by
Gisquet [12]	Changes in personality and loss of control over one's life and illness
Synofzik & Schlaepfer [26]	The 'level' and 'extent' of changes to naturalistic notion of personality
Focquaert & De Ridder [27]	Changes in personality and self-perception
Glannon [6]	Changes in thought and personality
Schechtman [3]	Narrative identity and agency/disruption of the narrative flow
Klaming and Haselager [28]	Disruptions of psychological continuity impact on patient competence and responsibility
Johansson et al. [22]	Personality changes and impacts on authenticity
Schermer [23]	Balancing risks and benefits and respect for autonomy and responsibility
Baylis [29]	Disruption of the balance between how a person sees and understands herself with how others see and understand her
Nir & Walter [30]	Personal identity and a sense of free agency (identification)
De Haan et al. [13]	Patients experience a richer field of affordances and act more flexible on these new affordances
Witt et al. [4]	Patients' core attitudes
Gilbert [31, 32]	Self-estrangement, loss of control and powerlessness.
Kraemer [33]	Felt-Authenticity and felt-Alienation
Mecacci & Haselager [34]	Psychological maladaptations and conceptual schemes concerning the relationship between mind and brain
Dings & de Bruin [35]	Aspects of the self – embodied, experiential, affective, intersubjective, psychological/cognitive, narrative, extended and situated
Maslen, Pugh & Savulescu [36]	DBS can potentially affect authenticity of the patient's choice.
Mackenzie & Walker [37]	Autonomy, competence
Nyholm & O'Neill [38]	DBS can bring about a patient's "true self": best version or the best part(s) of a person as valued from the point of view of the patient or from the point of view of a third party (e.g. the family).
Goddard [39]	The impacts of DBS must pay account to the interrelation of identity or agency or autonomy

effects on PIAAAS should differentiate between active and inactive control groups because there is a difference in the kind of effect estimates that are obtained [42].[8] It is essential to stress that these observations do not lead to the conclusion that case study designs are less valuable than RCTs in all respects.

According to a Global Deep Brain Stimulation Devices Industry report, in 2018, 21 companies are commercialising DBS worldwide[9]; Medtronic accounts for 150,000 implanted patients alone [44]. As such, accounting for the exact number of patients implanted with all different commercialized DBS devices worldwide is difficult to guess, but 150,000 is clearly an underestimation. Given the high number of patients

[8] This observation does not mean that for establishing causal relationships, there has to be a control group installed; having control groups is one example of good experimental design in order to compare effects. However, with regard to interventional DBS studies on cognitive changes, a recent review outlined that the majority of such studies is actually under-powered thereby affecting the inferences that can be drawn from such results (i.e. studies lacked statistical power even for large effect sizes and therefore are associated with an increased type II error risk [43]) Effect size refers to a standardized measure that quantifies the size of the difference between two groups or the strength of association between two variables (i.e. the magnitude of the effect). It goes without saying that studies on the presumed effects of DBS on PIAAAS should also be adequately powered. We are aware of the fact that recruiting age-, medication- and disease-matched controls and adherence to robust study designs are often practically difficult. A more detailed discussion on study designs (including, for example, interventional pre-post analyses), however, is beyond the scope of this article

[9] These companies include Boston Scientific Corp., Abbott Laboratories, Aleva Neurotherapeutics SA, Deep Brain Innovations LLC, Beijing Pins Medical Co. Ltd., etc. They are commercialising and manufacturing their devices across US, Canada, Japan, Europe, Asia-Paficic, Latin America. Please refer to https://www.prnewswire.com/news-releases/global-deep-brain-stimulation-devices-industry-300594349.html Last retrieved May 06 2018.

implanted with DBS, the number of reported (putative) DBS-induced PIAAAS changes appear to be extremely low. Cumulatively, our study found that there were only 168 patients interviewed across the 8 first-hand primary studies. Even if we were to include the 13 marginal and case reports we found, it would not significantly change the prevalence of evidence.[10]

The putative effects of DBS on patients' PIAAAS has probably been inflated in several ways. First, there is the problem of scarce data given that a large proportion of the published studies involve reports of only marginal or singular cases, and it is not possible to derive conclusions from this basis for explaining the phenomenology of DBS. For instance, a scholar who has read reports of marginal findings that some patients experience mood changes following DBS implantation might extrapolate that these mood changes are evidence of postoperative PIAAAS changes, even though mood changes are not sufficient to the ascription of DBS induced changes on PIAAAS. Deriving conclusions from marginal cases might lead to committing a *post hoc ergo propter hoc*-related error [9]. The phenomenon of "becoming a different person" after DBS interventions could not be solely attributed to the electrical stimulation itself but also to post-operative treatment adjustments or to disease progression [47, 48]. As such, the prevalence and incidence of effects on PIAAAS might not be exclusively correlated with a specific DBS target and/or stimulation parameter. It should rather be seen as a result of the interaction between electrical stimulation, adjustments in medication, and natural progression of the disease [9 47–49], apart from premorbid personality traits and e.g. the pre-operative psychosocial status of the individual [47], especially when DBS is used in patients with neurodegenerative disorders where changes to PIAAAS are naturally inevitable regardless of treatment course and choices. For instance, although Parkinson's disease is usually associated with motor symptoms such as bradykinesia, rest tremor, muscular rigidity, and postural instability, a large proportion of affected individuals also exhibit cognitive impairment and psychiatric symptoms [50]. Studies show that almost 25.2 to 40% of Parkinson's disease patients suffer from depression, up to 43% have anxiety disturbances, 32 to 42% exhibit apathy, 5.6 to 11.1% experience mania or hypomania, 15% have symptoms of impulse control disorders [51, 52], up to 75% complain of insomnia [53], 8 to 40% experience psychosis [54], and as many as 78.2% develop dementia [55]. Some of these disorders such as depression, anxiety disorders, apathy, and cognitive impairment might be due to the degeneration of brain structures leading to complex brain signalling disturbances caused by Parkinson's disease itself [51, 56, 57], whereas others such as mania/hypomania, impulse control disorders, and psychosis might, to a greater degree, result from dopaminergic medication used to treat motor symptoms [52, 53]. Most of these disorders are associated with multiple risk factors, and their onset and progression are determined by a combined effect of genetic susceptibility, neural degeneration, neurotransmitter dysregulation, co-existing psychiatric disorders, and medication dosage and regime [54, 58, 59]. Hence, changes in PIAAAS following DBS should not only be attributed to the DBS target structure, surgical trajectory, and stimulation parameter, but should also take into account patient history, disease attributes, and other forms of treatment adaptations such as medication adjustments. At this point in time, it is relatively difficult to isolate the cause of these post-operative changes, though they have been associated with DBS. Connected to this point is the concern that no generalizable conclusions and recommendations should be drawn from such limited data.

Second, there is a fundamental problem with empirically investigating effects of DBS on PIAAAS. As it was outlined previously [47], there are currently only a small number of scales that are trying to measure personality-related changes (for studies investigating "agency" [60, 61]). Unfortunately, a number of these scales may generate biased and/or insufficient responses because they often refer to self-report measurements. Moreover, a majority of them are test-psychologically inappropriately verified (regarding all necessary measurement criteria, e.g. reliability & validity) and do not consistently take up recent insights from psychological research (i.e. they focus on explicit-deliberate processing entirely). Finally, they rarely take up responses from third parties (e.g. spouses, relatives) that could substantially contribute to our understating of undesired changes following DBS interventions. Consequently, there are currently only vague objective markers of e.g. personality (gathered via e.g. the big five personality test) and

[10] With or without marginal case reports, our position would be similar: empirical evidence suggesting a link between DBS and PIAAAS is rare. This echoes Temel et al.'s [45] metareview where they report "personality changes, hypersexuality, apathy, anxiety, and aggressiveness were observed in less than 0.5%" of DBS outcomes "and only reported in case studies". It is crucial to note that Temel et al. [46] do not provide specific proportion of "personality changes" within the 0.5%.

only few studies that have investigated on the topic (thereby generating only few data). Similar to the difficulties that arise when dealing with "personality" as a rich psychological concept, "identity", "agency", "authenticity", "autonomy" and "self" constitute even more difficult concepts from an empirical perspective. Representing multifaceted and ambiguous constructs, these terms are far from ideal for an empirical investigation because operationalization is difficult. Whilst there are numerous studies focusing on various subsets of what could be termed "personality", such as cognitive deterioration and changes in mood, to name a few, some of the terms related to PIAAAS seem not particularly suited for quantitative inquiries.[11] Because it is a vital prerequisite of empirical studies to generate concise research questions on clearly identifiable markers to meet common methodological quality criteria, it is likely that concepts such as "authenticity" and the "self" will probably remain for some time in the philosophical rather than in the empirical domain. This is not to say that with time, no better measures of PIAAAS will be developed and that investigating subsets of the latter relating to e.g. changes of affect can and will contribute to our understanding of more qualitative concepts. Also, this does not imply that ethical analysis only makes sense when neuroscience gets in that stage of complete operationalization of psychological concepts. Neuroethicists do not have to wait for neuroscience to be finished before they can contemplate on its ethical implications [28]. We are also not trying to suggest that neuroethicists can base their work only in response to neuroscientific empirical work. However, it is currently difficult to assess the degree of change to patients' PIAAAS after DBS implantation given the scarcity of instruments to objectively assess changes of PIAAAS.

Consistent with what has been said in the previous paragraph, our third point regarding the inflation of putative effects of DBS on patient PIAAAS takes up methodological prerequisites (mostly stemming from sociology) of qualitative research. Briefly, whilst single quotes of patients can be illustrative, they need to be treated with caution. Convergence of responses representing saturation of the data should be in place before generalizing the outcome(s). Needless to say, qualitative studies should disclose the methodological details to allow interested readers to understand them. Finally, the concept of "understanding" in qualitative research is a decisive issue that should be reviewed during the process of interviewing, analysing, and writing. Patient experiences and narratives, which should unquestionably be heard, bring fundamental knowledge to our comprehension of postoperative changes in the context of DBS. However, marginal or single case reports, do not inform us of the actual incidence of DBS-induced effects on the PIAAAS in a particular population of patients treated with DBS. In some cases, marginal or single case reports could even bend the focus in the second- and third-hand literature about changes to patient PIAAAS that, although warranting important medical and ethical consideration, could inflate potential adverse effects, way beyond what would be observed if a systematic study was conducted. Although, subjective narratives may allow to understand some aspects of the potential phenomenon of DBS-induced PIAAAS [9, 63] and some critical ethical issues, quantitative empirical studies with strong research-designs constitute an appropriate tool to investigate causal effects and to inform us about the incidence of a given variable following a certain treatment.

Finally, some have made the claim that the DBS literature does not address or publish enough negative outcomes [64–66]. If this is the case, then it would mean that the limited amount of evidence of DBS effects on patient PIAAAS may be due to lack of negative reports. In that respect, it is important to consider whether most studies have been designed to include all dimensions of DBS's potential side effects. Should study designs neglect inclusion of subjective reports, then a lack of evidence would not be evidence of a lack; it would simply reflect that studies are not designed to capture all aspects of a potential phenomenon. Concomitantly, there is also a possibility that some patients do not report their subjective experiences. Hariz and Hamberg have observed that most implanted patients considered their side effects to be the trade-off between getting treatment and having control of the symptoms enabling them to be more active in day-to-day life while incurring with postoperative slurred speech or balance problems [67]. As well, there are no objective means of deciding when a treatment has to be considered a failure or a success [68]. Although scales and measures that can assess improvement or deterioration in certain symptoms of

[11] Providing evidence for empirical (correlative or causal) relations between DBS and PIAAAS might be beyond the ability of qualitative research: "Phenomenological approach cannot establish statistical relationships, because it is concerned with uniqueness and individuality, rather than numbers and statistics" [62].

neurological and psychiatric disorders exist, it is to some extent up to the patient and/or family members to decide whether the treatment is a success or not, likely on how benefits outweigh side-effects and whether they are in line with the patient's and family members' needs and expectations. It is also important to highlight that what can be deemed successful from a patient's perspective might not necessarily be deemed successful by the family. Although both the patient and family members might see relief from motor symptoms, a patient might not see potential treatment-associated hypomania as much of a nuisance as his or her family members would. This highlights that although PIAAAS changes might occur, they should not necessarily be seen as a treatment failure, automatically regarded as something completely negative, or viewed as a trade-off that a patient should not make.

Limitations of the study

A possible limitation of the study, even though simultaneously strengthening our primary claim, can be found in the practice of selectively searching for PIAAAS in the empirical literature. On the on hand, if instead of only searching for DBS, we had searched (more broadly) with terms such as neurotechnologies, brain implants, neural devices, etc., then we would have found a greater number of theoretical articles. On the other hand, as outlined previously, PIAAAS are philosophical concepts that are inherently non-scientific. Even though empirical investigations using the concepts of "personality" and "agency" do exist, they often do not fully capture the philosophical essence of these terms. For instance, autonomy is sometimes medically defined, especially in the Parkinson's literature, as the ability to perform a particular set of actions associated with daily living [69]; by comparison, the concept is portrayed more broadly in the philosophical literature. In most neuroethics and bioethics publications, the conditions for autonomy include (1) intentions (volitions), (2) competence (capacity to appreciate right and wrong and determine oneself accordingly), (3) absence of external controlling influences (freedom from external forces), and (4) absence of internal controlling influences (freedom from internal coercive influences) [70, 71]. Therefore, it is obvious that our sample of the empirical literature on PIAAAS in a wider sense is too conservative. The search terminologies we used, which are mainly based on philosophical discourse, might not have fully captured the extent of PIAAAS-associated key words and terms as used in medical databases. Accordingly, a large number of studies were lost due to the rather narrowly defined search string. However, since the vast majority of the theoretical neuroethics literature refer to PIAAAS specifically—concepts that have weak empirical grounding—corroborates our claim that neuroethics is in danger of discussing PIAAAS-related problems without a rigorous empirical foundation; as a consequence, buying into speculative ethics. This does not mean that we neuroethicists are not allowed to take anecdotal findings in order to make a more general (thus speculative) philosophical point. However, we should accept that by not explicitly stating the weak empirical grounding of our claims, we increase the risk of inflating an empirically impenetrable speculative bubble and even more pressingly, disseminating information that might detrimentally affect the decision making of some prospective patients and their relatives who would benefit from treatment. Again, we are not advocating that philosophers should restrain from engaging in philosophically interesting theoretical reasoning stimulated by an anecdotal incident or that potential postoperative DBS changes experienced by patients are not critical ethical concern despite the low number of first-hand primary studies and large number of marginal and single case reports. Whether and in which cases philosophy should be based on empirical data, albeit an intriguing question, is not within the scope of this work. Although it is important to acknowledge the occurrence of these potential DBS-induced PIAAAS changes and to devise measures to adequately address them, they must also be viewed in light of incidence rates in order to better inform patients, family members, and caregivers of actual risk probabilities associated with this surgical intervention. Unquestionably, the measurement problem of complex changes such as PIAAAS makes the assessment of incidence rates extremely difficult, and in some cases, perhaps even impossible.

Conclusion

We have argued that there is a critical lack of primary empirical studies corroborating potential DBS-induced effects on patients' postoperative PIAAAS. We have observed a disproportionate relationship between what is available in terms of supporting empirical evidence and the number of theoretical interpretations and

assumptions canvassed by neuroethicists despite the thinness of any empirical backing of their claims concerning the impact of DBS on patient PIAAAS. To our view, this is reflective of a speculative neuroethics bubble, which may need to be deflated. Occurences of "ethics hype" and "speculative ethics" are also discusses in other domains of ELSI literatures [72–76].

While we support the view that theoretical neuroethics is as an important field of research, we question the robustness of building philosophical accounts on limited empirical evidence (often only with very selective quotes of patient self-reports). Given the current state of the neuroethics literature as analysed in this study, most claims by neuroethicists concerning the effects of postoperative DBS PIAAAS-related changes are made up of conclusions derived from first-hand primary studies that do not include control groups, or from anecdotal reports, thereby risking that the stories seem to be 'cherry picked'. Even if a large proportion of the published theoretical neuroethics manuscript appears to be supported by scarce data from which it is not possible to derive conclusions, potential postoperative DBS changes experienced by patients remain a critical ethical concern. Neuroethicists play a crucial role in addressing concerns of stakeholders (including patients and the general public) and improving philosophical understanding of such concepts.

However, there is a pressing and urgent need to examine the question of the effects of DBS on PIAAAS with "fresh" evidence. Publishing more first-hand primary studies can only enhance the reliability, robustness, and validity of the discipline. Epistemological and methodological challenges can be overcome by developing instruments to measure potential changes in PIAAAS. Hence, we recommend facilitating the development of instruments that will become an international standard for capturing postoperative variations in patient experience of post operative changes to PIAAAS. Responsibility to study further this question should also be taken by relevant stakeholders from the device industry, including device companies. To avoid risks of conflicts of interest(s), the stakeholder should provide necessary financial support to independent institutions to develop study protocols that will investigate more extensively issues related to DBS-associated impacts on patients' PIAAAS.

Reading that "the risk of becoming another person following surgery is alarming" [4] and that "personality changes represent a threat to personal identity and agency" [3] is not without consequence; particularly for prospective patients (and families) who could immediately and directly benefit from the intervention. These neuroethical assertions come with risks: they may perpetuate and propagate misleading assumptions that lack strong supportive scientific evidence. Ethics that propounds such unfounded speculation may seem to encourage the public, but most importantly prospective patients, to adopt a reluctant approach to treatment [-25]. However, despite the empirical limitations, we believe investigating further these issues help patients to be informed about the potential risks of psychiatric adverse events, possible changes in personality, and other treatment-associated changes at hand. Neuroethics has a fundamental responsibility to play in articulating risks about the putative effects of DBS on PIAAAS, hence more research and funding are needed. Nonetheless, we, the neuroethicists, should also keep in mind our responsibility to properly inform our readers (potentially, prospective patients) of actual risks, acknowledging that our views are more than likely based on limited case reports. We should also work to ensure that patients and their family members are neither hyped up by overly positive depictions of DBS (notably by media), nor turned down by hyperinflated assumptions about the involved associated risks. The media account for bigger responsibilities in how the effects of DBS are portrayed to the public. Neuroscientists should receive appropriate media training so as to critically and effectively counter stories involving hype, unrealistic and inflated sensationalistic portrayals of DBS [77].

A lack of evidence of putative effects of DBS on PIAAAS is not evidence that there is no link; empirical studies are most likely not designed to capture all aspects of potential DBS-induced PIAAAS phenomena. What remains unclear is whether it is all DBS-implanted patients who are at risk of postoperative PIAAAS sequelae. Further neuroethical research is needed more than ever, especially in a context where novel generation of DBS systems including closed-loop, artificially intelligent implants, and brain-computer interfaces are being developed. [78–85] Whether or not these emerging neurotechnologies will affect PIAAAS is still uncharted territory.

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Compliance with ethical standards

Competing interests None.

Annex 1: Search Methods Employed

I. We searched the top 30 bioethics journals (according to a list provided by bioethics.net) and AJOB Neuroscience.

Name of journals:

Am J Bioethics (The American Journal of Bioethics)
Dev World Bioeth (Developing World Bioethics)
Hastings Cent Rep (Hastings Center Report)
Ethnic Health (Ethnicity & Health)
J Med Ethics (Journal of Medical Ethics)
BMC Med Ethics (Biomed central Medical Ethics)
Bioethics
Neuroethics-Neth
J Empir Res Hum Res (Journal of Empirical Research on Human Research Ethics)
Public Health Eth-UK (Public Health Ethics)
J Law Med Ethics (The Journal of Law, Medicine & Ethics)
Account Res (Accountability in Research)
J Bioethic Inq (Journal of Bioethical Inquiry)
Med Law Rev. (Medical Law Review)
Rev. Rom Bioet (Revista Romana de Bioetica)
Genet Counsel (Journal of Genetic Counseling)
Ethik Med (Ethik in der Medizin)
Acta Bioeth (Acta bioethica)
Nursing Ethics
Journal of Medicine and Philosophy
Medicine, Health Care and Philosophy
Nanoethics
Theoretical Medicine and Bioethics
The Journal of Clinical Ethics
HEC Forum
Cambridge Quarterly of Healthcare Ethics
American Journal of Bioethics Primary Research
Indian Journal of Medical Ethics
Asian Bioethics Review
International Journal of Feminist Approaches to Bioethics
AJOB Neuroscience.

II. Philosophy databases

Search until May 2, 2017
ProjectMuse
JSTOR
PhilPapers
PhilIndex (linmited search to academic journals)

III. Scientific, psychology, and psychiatry databases combined

Search until May 3, 2017
PubMed - 208 results
Scopus - 236 results
Embase (via Ovid) - 263 results
Web of Science - 157 results
PsycAarticles - 17 results
Psychology & Behavioral Sciences Collection (PBSC) - 16 results
PsycInfo (via Ovid) - 122 results
Psychiatry Online - 139 results (excluded news articles)

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SECTION III.

Neuroethics Publications on Deep Brain Stimulation for Alzheimer's Disease

The next three chapters are comprised of three peer-reviewed manuscripts (one paper per chapter) in which John Noel M. Viaña is the first and corresponding author:

Chapter 4, pages 129 to 137:

Viaña, JNM, Vickers, JC, Cook, MJ & Gilbert, F 2017, 'Currents of memory: recent progress, translational challenges, and ethical considerations in fornix deep brain stimulation trials for Alzheimer's disease', Originally published in *Neurobiology of Aging* by *Elsevier*, vol. 56, pp. 202-210. doi: 10.1016/j.neurobiolaging.2017.03.001. Available from: https://www.sciencedirect.com/science/article/pii/S0197458017300726?via%3Dihub

Chapter 5, pages 138 to 150:

Viaña, JNM, Bittlinger, M & Gilbert, F 2017, 'Ethical Considerations for Deep Brain Stimulation Trials in Patients with Early-Onset Alzheimer's Disease', Reprinted from the *Journal of Alzheimer's Disease* with permission from the *IOS Press*, vol. 58, no. 2, pp. 289-301. doi: 10.3233/JAD-161073. Available from: https://content.iospress.com/articles/journal-of-alzheimers-disease/jad161073

Chapter 6, pages 151 to 170:

Viaña, JNM & Gilbert, F 2018, 'Deep brain stimulation for people with Alzheimer's disease: Anticipating potential effects on the tripartite self', Originally published in *Dementia (London)* by *Sage Journals*, p. 1471301218761147. Available online first, published on March 11, 2018. doi: 10.1177/1471301218761147. Available from: http://journals.sagepub.com/doi/full/10.1177/1471301218761147#_i1

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Review

Currents of memory: recent progress, translational challenges, and ethical considerations in fornix deep brain stimulation trials for Alzheimer's disease

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ABSTRACT

The serendipitous discovery of triggered autobiographical memories and eventual memory improvement in an obese patient who received fornix deep brain stimulation in 2008 paved the way for several phase I and phase II clinical trials focused on the safety and efficacy of this potential intervention for people with Alzheimer's disease. In this article, we summarize clinical trials and case reports on fornix deep brain stimulation for Alzheimer's disease and review experiments on animal models evaluating the physiological or behavioral effects of this intervention. Based on information from these reports and studies, we identify potential translational challenges of this approach and determine practical and ethical considerations for clinical trials, focusing on issues regarding selection criteria, trial design, and outcome evaluation. Based on initial results suggesting greater benefit for those with milder disease stage, we find it essential that participant expectations are carefully managed to avoid treatment disenchantment and/or frustration from participants and caregivers. Finally, we urge for collaboration between centers to establish proper clinical standards and to promote better trial results comparison.

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide (Plassman et al., 2007), with 5.3 million AD-affected individuals in the USA alone (Alzheimer's Association, 2015) and more than 95% of whom are ≥65 (Hebert et al., 2013). Characterized by brain pathological hallmarks such as β-amyloid plaques and neurofibrillary tangles, AD clinically manifests as slowly progressive dementia and gross cerebral atrophy (Bird, 1998). Currently, AD is divided into asymptomatic preclinical, predementia, and dementia phases (Jack et al., 2011), with increasing cognitive deficits associated as the disease progresses to later stages. In the dementia phase of AD, affected individuals experience deficits in memory, reasoning and executive function, visuospatial abilities, language functions, and/or personality, which significantly interfere with ability to function at work or at usual activities (McKhann et al., 2011). Death usually results from general inanition, malnutrition, and pneumonia (Bird, 1998).

Currently, only 6 drugs have been approved by the FDA for the management of AD, but none of them prevents disease progression (Alzheimer's Association, 2015), treats the underlying pathology, or provides long-lasting benefit (Broadstock et al., 2014). As such, several novel drug (Kumar et al., 2015) and non-drug approaches (Corbett and Ballard, 2012) are currently being tested, with several non-drug approaches being invasive in nature (Nilsson et al., 2010; Tuszynski et al., 2015). Among the invasive neurosurgical methods that is being tested for AD is deep brain stimulation (DBS), which involves implanting in a region of interest one or more quadripolar leads that are then connected to an externally programmable implanted pulse generator to deliver continuous electrical stimulation (De Jesus et al., 2015; Gionfriddo et al., 2013; Okun, 2012). DBS stimulation parameters are programmable, and clinicians determine the optimal settings and implantation location for each patient to maximize relief from disease symptoms while minimizing unwanted stimulation-induced side effects such as speech

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disturbance (Patel et al., 2015), depression, and suicidality (Appleby et al., 2007). DBS could exert its therapeutic action by inducing orthodromic or antidromic effects that change patterns of neuronal activation and inhibition and potentially disrupt abnormal firing patterns at the synaptic level. These could then lead to changes in neurotransmitter release, neuronal excitability, and in oscillatory properties of connected neural networks (Deniau et al., 2010; Hammond et al., 2008). DBS in certain brain regions has already been approved for several indications such as essential and Parkinsonian tremor, Parkinson's disease, dystonia, obsessive compulsive disorder, and epilepsy (Sarem-Aslani and Mullett, 2011).

Most clinical trials of deep brain stimulation for people with Alzheimer's disease targeted the fornix, a white matter bundle that serves as the major hippocampal output tract (Thomas et al., 2011), connecting the hippocampus with the mammillary bodies in the hypothalamus, septal nuclei (Mielke et al., 2012), and nucleus accumbens (Oishi and Lyketsos, 2014). The fornix is located in the medial diencephalon and is an integral part of the Papez circuit, which is also referred to as the "temporal lobe memory system" (Nowrangi and Rosenberg, 2015). Damage of the fornix in humans and animals has been associated with anterograde amnesia, deficits in spatial memory, and impairment in visuospatial memory acquisition, indicating the fornix's role in declarative memory formation and consolidation (Thomas et al., 2011). In people with AD, the fornix is atrophied and displays microstructural impairments in the form of dendritic and axonal damage and breakdown of myelin and tissue cytoarchitecture, which correlate with worse performance on memory tasks (Douet and Chang, 2014; Mielke et al., 2012).

Given the invasive nature of DBS compared with other existing and proposed therapies for AD, it is important to examine current clinical trials (Table 1) and animal studies (Table 2) of fornix DBS for AD to evaluate and appraise the current level of evidence, determine relevant translational and ethical issues, and provide recommendations for ongoing and future trials to prevent unnecessary harm and ensure that trial participants are well-protected and adequately informed.

2. Deep brain stimulation of the fornix in humans and animals

2.1. Experimental trials in humans

The potential of fornix DBS for memory improvement was first identified when autobiographical memories were evoked and improvements in verbal and visuospatial memories were observed in a patient who underwent DBS for obesity (Hamani et al., 2008). Since the fornix is a major output pathway for the hippocampal formation (Thomas et al., 2011), and hippocampal damage is an early feature of AD (Moodley and Chan, 2014), this discovery led to a phase I clinical trial in 6 people with early AD. During surgery, 2 subjects reported stimulation-induced autobiographical experiential phenomena. Memory improvements were also reported in some participants after 12 months of stimulation, especially in those who experienced vivid experiential phenomena during surgery and had less severe memory problems (Laxton et al., 2010). Increased metabolism in certain brain networks (Smith et al., 2012) and increased hippocampal volume in 2 participants (Sankar et al., 2015) were also observed 12 months after the stimulation.

Taking into account the results of the phase I trial (Laxton et al., 2010), a phase II clinical trial was then initiated (Holroyd et al., 2015). The phase II "ADvance" trial is a randomized, double-blind, placebo-controlled, delayed-start trial conducted in different sites in North America. In this study, half of the subjects did not receive any stimulation for 12 months, whereas the other half received continuous DBS stimulation. All participants were then stimulated after the 12-month period. An initial report assessing the surgery's safety indicated that accurate targeting of the fornix without direct injury was successfully performed, and that 90 days postsurgery, bilateral fornix DBS was well tolerated by the trial participants (Ponce et al., 2016). The first-year results of the ADvance trial showed an interesting trend in cognitive change only when results were separately analyzed for participants younger and older than 65. After 1 year of DBS, participants <65 appeared to have significantly worse cognitive scores than controls <65, whereas participants ≥ 65 exhibited slight improvement (Lozano et al., 2016).

In addition to the studies done in North America, another team in France has performed bilateral fornix DBS. The subject's cognitive performance stabilized over 2 years of continuous stimulation, and her anxiety and mood were slightly improved and were eventually stabilized after 6 months of stimulation (Fontaine et al., 2013, 2015).

2.2. DBS of the fornix in animal models

Several studies in animals (Table 2) have also been conducted to elucidate the effect of fornix DBS on cognition and behavior (Hao et al., 2015; Hescham et al., 2013, 2017; Zhang et al., 2015), brain activity (Gondard et al., 2015; Hao et al., 2015; Hescham et al., 2016; Ross et al., 2016; Talakoub et al., 2016), and brain structure (Hao et al., 2015; Hescham et al., 2017). Results from these studies indicate that fornix DBS improves spatial (Hao et al., 2015; Hescham et al., 2013, 2017; Zhang et al., 2015), contextual (Hao et al., 2015), and recognition (Zhang et al., 2015) memories with no effect on locomotion, anxiety, pain threshold, and motor learning levels (Hao et al., 2015; Hescham et al., 2013; Zhang et al., 2015). These suggest that fornix DBS could improve both hippocampus-dependent spatial and hippocampus-independent recognition memories (Zhang et al., 2015). In addition, fornix deep brain stimulation also results in increased neuronal activity, determined by enhanced cFos expression (Gondard et al., 2015; Hao et al., 2015; Hescham et al., 2016); evoked hippocampal responses (Talakoub et al., 2016); increase in hippocampal acetylcholine (Hescham et al., 2016); induction of proteins involved in axonal growth, and guidance, synaptic plasticity, synaptogenesis, and neuronal differentiation and survival (Gondard et al., 2015); enhanced long-term potentiation (Hao et al., 2015); dopamine release in the nucleus accumbens; and induction of medial and corticolimbic hemodynamic responses via glutamatergic and dopaminergic transmission (Ross et al., 2016). DBS could also potentially enhance hippocampal neurogenesis; however, results from different studies are conflicting (Hao et al., 2015; Hescham et al., 2017). Finally, Talakoub et al. (2016) demonstrated that closed-loop low-frequency stimulation during hippocampal sharp-wave ripples could result in the interruption of these ripples and associated multi-unit activity.

3. Translational challenges of animal studies

Currently, there is no wild-type or transgenic model that replicates the full suite of pathological changes in AD, nor the typical spread of pathology from medial temporal regions to other cortical areas. Consequently, evaluating the effects of stimulation of axons in the fornix in models that are currently available may provide an incomplete profile of potential benefits in human AD. However, there have been some intriguing results from animal studies that indicate that the benefits of DBS may be more widespread than anticipated from stimulating simply this axonal tract given the observed effects on neurogenesis (Hao et al., 2015; Hescham et al., 2017), synaptic and neuroprotective protein expression (Gondard et al., 2015), and synaptic properties (Hao et al., 2015), potentially suggesting that DBS could have a broader neuroprotective function in neural cell biology. It will be important to ensure the validity of

Table 1
Human studies on deep brain stimulation of the fornix for Alzheimer's disease and obesity

Study	Case study—obesity (Hamani et al., 2008)	Phase 1—Canada (Laxton et al., 2010; Sankar et al., 2015; Smith et al., 2012)	Phase 1—France (Fontaine et al., 2013)	Phase 2—North America (Holroyd et al., 2015; Lozano et al., 2016; Ponce et al., 2016)
Participants	1	6	1	42 (21 in ON and 21 in OFF)
Age range	50	51–69	71	45–85
Condition	Morbid obesity	Probable AD (1983 NINCDS-ADRDA)	AD DSM IV criteria for AD	Probable AD (2012 NIA/AA)
Initial cognitive score	Average to high in all domains	MMSE: 22.3	3 mo pre-surgery MMSE: 23, ADAS-Cog: 12.25 7 d pre-surgery MMSE: 29, ADAS-Cog: 9	ON: ADAS-Cog 13: 28.6, CDR-SB: 4.0 OFF: ADAS-Cog 13: 27.1, CDR-SB: 3.6
Stimulation parameters	2.8 V, 130 Hz, 60 μs	3.0–3.5 V, 130 Hz, 90 μs	2.5 V, 130 Hz, 210 ms	3.0–3.5 V, 130 Hz, 90 μs
Cognitive, psychiatric, and QoL test results	↑ in CVLT, SALT, WAIS AI, Recollection-based recognition in the AWRT	ADAS-Cog: ↑ in 4/6 participants after 6 mo; ↑ in 3/6 after 12 mo, average ↑ of 4.2 points; MMSE: ↑ of 2 points to ↓ of 8 points, ↓mean decline rate from 2.8 to 0.8 points; QoL: 2 to 5 ↑	Return to initial cognitive level 12 mo post-surgery. ADAS-Cog: 9.91; MMSE: 24	ADAS-Cog 13: <65, ON > OFF by 10.3 ± 6.1 points; ≥65, OFF > ON by 4.1 ± 2.6 points CDR-SB: <65, ON > OFF by 3.5 ± 0.7 points ($p < 0.001$), ≥65, OFF > ON by 1.4 ± 1.0 points
Neurologic test results	sLORETA: ↑ in ipsilateral mesial temporal lobe	PET: ↑ temporal and parietal lobe; sLORETA: ↑ ipsilateral mesial temporal lobe structures; MRI: ↑ hippocampal volume (2 patients)	PET: ↑ mesial temporal lobe	PET: all ON, ↑ temporal and parietal brain regions; all OFF, slight ↓ all regions; ≥65, ↑ ON group; <65, ↓ metabolism for both ON and OFF
Safety	No mention of any AE	Surgery well tolerated, and no participant required hospitalization	Surgery well tolerated, and no perioperative complication; no clinical or biological AE except increase in irritability	No neurological deficits, no acute cognitive AEs, no deaths; 3 long-term serious therapy-related events in 1 OFF participant; independent DSMB: AE safety profile was as expected

Key: ADAS-Cog, Alzheimer's Disease Assessment Scale—cognitive component; AE, adverse events; AWRT, Associative Word Recognition Task; CDR-SB, clinical dementia rating—sum of boxes; CVLT, California Verbal Learning Test; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSMB, data and safety monitoring board; MMSE, Mini–Mental State Examination; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging-Alzheimer's Association; NINDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA); OFF, participants that did not receive stimulation for 1 year; ON, participants that received stimulation for 1 year; PET, positron emission tomography; QoL, quality of life; SALT, Spatial Associative Learning Test; sLORETA, Standardized Low-resolution Electromagnetic Tomography; WAIS AI, Wechsler Adult Intelligence Scale Attention Index.

Table 2
Animal studies on deep brain stimulation of the fornix

Study	Subjects	Stimulation parameters	Assessments	Results
Hescham et al. (2013)	Adult male SD rates injected with scopolamine 10 fDBS, 11 sham	Bilateral, 10/100 Hz, 50/100/200 μA, 100 μs; 2 min before and until the end of each session	Behavior (OLT and OFT)	↑: OLT (memory performance) NSD: OFT
Hescham et al. (2016)	Male SD rats 15 fDBS, 11 sham	Bilateral, 100 Hz, 100 μA, 100 μs; cFos and dialysis: 1 h	Brain activity and neurotransmitters (Ach and Glu) released	↑: cFos expression in CA1 and CA3 subregions; hippocampal Ach in first 20 min of stimulation NSD: Glu levels
Gondard et al. (2015)	Adult male Wistar rats 27 fDBS, 27 sham	Bilateral, 130 Hz, 2.5 V, 90 μs; 1 h	Protein expression in the hippocampus	↑: Hippocampal cFos (dentate gyrus granule cell layer), BDNF, VEGF, synaptic proteins GAP43, and synaptophysin NSD: APP, tau, ptau, and chaperone proteins
Zhang et al. (2015)	6-wk old SD rats injected with Aβ 1-42 peptides in the hippocampus 8 fDBS, 8 sham	Bilateral, 130 Hz, 500 μA, 90 μs; 24 h	Behavior (MWM, NORM, OFT)	↑: MWM (reference memory of platform, frequency of platform crossings, time spent in platform quadrant); NORM (time with novel object and recognition index) NSD: OFT
Hao et al. (2015)	6 to 8-wk old female RTT (Mecp2+/−) mice 111 fDBS; 106 sham[a]	Unilateral, biphasic rectangular pulses, 130 Hz, 60 μs, 80% intensity needed for hippocampal afterdischarge; 1 h per d for 14 d	Behavior (MWM, FM, OFT, light-dark box, wire hang, dowel walk, accelerating rotarod, 3-chamber interaction, pain threshold), synaptic transmission, brain activity, and neurogenesis	↑: MWM (memory in WT and RTT mice, retrieval in RTT mice); FM (contextual memory in WT and RTT mice; hippocampal infusion of atropine, an Ach receptor antagonist, did not alter fear memory in fDBS RTT or WT mice); LTP in WT and RTT mice; Fos expression in dentate neurons; bilateral dentate neurogenesis in WT and RTT NSD: OFT, light-dark box, wire hang, dowel walk, accelerating rotarod, 3-chamber interaction, pain threshold; baseline synaptic transmission ↓: slightly in magnitude of evoked responses in RTT animals
Hescham et al. (2017)	SD rats 10 fDBS, 7 sham	Bilateral, 100 Hz, 100 μA, 100 μs; 4 h	Behavior (MWM) and neurogenesis	↑: MWM (number of crossings in former platform location) NSD: hippocampal BrdU/NeuN double-labeled cells (no enhanced neurogenesis)
Ross et al. (2016)	Domestic swine 17 fDBS	Unilateral, biphasic, 3/5/7 V pulses, 130 Hz, 150 μs; fMRI: 5 6-s epochs with 1-min intervals and 10-min rest, FSCV: 1 6-s stimulation, 5-min rest	Brain activity and dopamine release	↑: medial limbic and corticolimbic circuits activity; biphasic NAc dopamine release in the NAc Intracranial NAc infusion of dopamine or glutamate receptor antagonists attenuated DBS-induced activity in the hippocampus and amygdala
Talakoub et al. (2016)	Adult female macaque 1 fDBS	Bilateral, biphasic, 100 μs; hippocampal response: 1/4/8 pulses, 1/2/3 mA, 1.75 Hz, 3 min; ripple interruption (closed-loop): 4 pulses, 2 ms, 2 mA when signal amplitude crosses threshold, 95 daily sessions: 50 min per session	Stimulation-induced hippocampal response and closed-loop-stimulation-induced interruption of hippocampal sharp-wave ripples	↓: hippocampal ripple duration through interruption of the tail of the ripple, multi-unit activity of interrupted ripples to below baseline levels, and ripple amplitude (as a result of closed-loop stimulation) Stimulation (4/8 pulses, 2/3 mA) evoked hippocampal response

Key: BDNF, brain-derived neurotrophic factor; BOLD, blood oxygen level-dependent; FM, fear memory; FSCV, fast scan cyclic voltammetry; LTP, long-term potentiation; MWM, Morris Water Maze; NAc, nucleus accumbens; NORM, Novel Object Recognition Memory Test; NSD, no significant difference GAP43, growth-associated protein 43; OFT, Open Field Test; OLT, Object Location Task; RTT, Rett syndrome; SD, Sprague Dawley; VEGF, vascular endothelial growth factor; WT, wild-type.
[a] Considering separate mice were used in each test.

current experimental results obtained since they could help inform decisions on trial design and participant selection. For instance, determining whether DBS of the fornix indeed induces neurogenesis or if it has a neuroprotective effect could help identify at which stage of AD fornix DBS might be most effective. In addition, it is important to ensure that the frequency and timing of stimulation provided is appropriate since it has been shown in a closed-loop protocol that DBS could interrupt hippocampal sharp-wave ripples, which play a role in memory consolidation and/or retrieval (Talakoub et al., 2016). Certain stimulation parameters and improperly timed stimulation should therefore be avoided as they could lead to memory impairment instead of improvement.

Results to date from the limited number of fornix DBS animal studies have been conflicting, as shown by differing results of

Table 3
Selection criteria for participant recruitment of human studies on deep brain stimulation of the fornix for Alzheimer's disease (primarily based on clinicaltrials.gov entries)

Study	Phase 1—Canada (Laxton et al., 2010)	Phase 1—France (Fontaine et al., 2013)	Phase 2—North America (Holroyd et al., 2015; Lozano et al., 2016)
Inclusion criteria			
Recruitment age	40–80	50–65 (extended to 70 after protocol amendment)	45–85
AD stage	Probable AD (1983 NINCDS-ADRDA)	AD DSM IV	Probable AD (2012 NIA-AA)
Cognitive score	CDR of 0.5–1, MMSE of 20–28	Episodic memory impairment from FCSRT/Grober and Buschke test; MMSE of 20–24	CDR of 0.5–1; ADAS-Cog 11 of 12–24, score ≥4 on item 1: immediate recall
Informed consent	Participant or surrogate	Participant	Subject, caregiver, and surrogate
Exclusion criteria			
Neurologic abnormalities	Pre-existing structural brain abnormalities (tumor, infarction, intracranial hematoma)	Abnormality on pre-operative MRI	Modified Hachinski ischemic score >4 at screening; history of brain tumor, subdural hematoma, or other clinically significant space-occupying lesions; history of head trauma
Cognitive abnormalities	-	-	Mental retardation
Psychiatric conditions	Other psychiatric diagnosis	Associated DSM IV axis I pathology	NPI 33 total score ≥10 or score ≥4 in any domain except apathy; YMRS ≥11; current major psychiatric disorder (such as schizophrenia, BD or MDD); active psychiatric disorder; score >10 on CSDD; current alcohol or substance use disorder as defined by DSM-IV-TR
Suicidality	-	-	Suicide past 2 y; C-SSRS
Additional tests			
Genetic screening or family check	-	-	-
Biomarker	-	MRI and/or CSF and/or PET proposed to participant	PET scans for characteristic metabolic pattern associated with AD

Key: ADAS-Cog, Alzheimer's Disease Assessment Scale—cognitive component; BD, bipolar disorder; CDR, Clinical Dementia Rating scale; CSDD, Cornell Scale for Depression in Dementia; CSF, cerebrospinal fluid measurement; C-SSRS, Columbia Suicide Severity Rating Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSM IV-TR, Diagnostic and Statistical Manual of Mental Disorders Text Revision; FCSRT, Free and Cued Selective Reminding Test; MDD, major depressive disorder; MMSE, Mini–Mental State Exam; MRI, magnetic resonance imaging; NIA-AA, National Institute on Aging-Alzheimer's Association; NINDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA); NPI, Neuropsychiatric Inventory; PET, positron emission tomography; YMRS, Young Mania Rating Scale.

potentially DBS-induced neurogenesis by the groups of Hao et al. (2015) and Hescham et al. (2017). Potential reasons may include differing stimulation parameters, investigation protocols, and animal models. For instance, both studies employed different stimulation frequencies, pulse widths, and stimulation durations (Table 2). Moreover, BrdU labeling was conducted by Hao et al. (2015) each day after DBS for 14 days, and mice were examined after almost 4 weeks in contrast to the study of Hescham et al. (2017) where rats were injected with BrdU for 3 consecutive days 3 days after stimulation and were sacrificed almost 6 weeks after. These differences simply illustrate that different protocols and animal models were used, which could account for potentially differing results.

Overall, these differences highlight the need to standardize stimulation parameters, and perhaps also animal models, in future animal experiments to better translate findings to mechanisms that are also present in people with AD. It is also important to note that most animal studies utilized pharmacological approaches (Hescham et al., 2013; Zhang et al., 2015) to produce memory impairments, and the effects of fornix DBS have not been examined in transgenic lines bearing human gene mutations linked to familial AD (Do Carmo and Cuello, 2013). The length of stimulation in all animal studies performed is also much shorter than those used in clinical trials, and thus, results from current animal studies might not fully reflect behavioral and physiologic changes associated with long-term DBS.

4. Ethical and practical considerations for clinical trials

4.1. Participant selection criteria

In the clinical trials (Holroyd et al., 2015; Laxton et al., 2010) and case studies (Fontaine et al., 2013) for DBS on people with AD, there was no uniformity of criteria employed in participant selection and consent acquisition (Table 3). Although most experimental participants were 50–65, one study was recruiting people as young as 40 (Laxton et al., 2010), whereas another one considered those who are up to 85 still eligible (Holroyd et al., 2015). Recruiting participants who are <65 and not reporting the conduct of any family background check and/or genetic screening could potentially allow the recruitment of people with a genetic mutation strongly predisposing them to AD that could have a more rapid disease progression and more pronounced brain pathology (Ringman et al., 2014). Moreover, early-onset dementia could also potentially include frontotemporal dementia as well as AD, unless this was specifically ruled out through the employment of neurologic and genetic tests (Rossor et al., 2010). Recruiting such participants could put them at risk and minimize potential benefits, especially in trials wherein stimulation is withheld for 1 year and if the same protocols are employed as for those with normal AD progression (Holroyd et al., 2015; Panegyres and Chen, 2013; Viaña et al., 2017). Different criteria for AD and different tests to evaluate baseline cognition were also used in each study. Also, although 2 (Holroyd et al., 2015; Laxton et al., 2010) out of 3 studies stated that participants should be on a stable dose of cholinesterase-inhibiting drugs, the period over which the drugs should have been taken differs between these studies.

Considering that DBS surgery and stimulation could lead to a number of neurologic and psychiatric adverse side-effects (Appleby et al., 2007; Patel et al., 2015; Pinsker et al., 2013), selecting the appropriate trial participants is of utmost importance to prevent unnecessary harms (Ovadia and Bottini, 2015). Almost all the studies excluded subjects with neurologic, psychiatric, and/or other medical abnormalities; however, only one (Holroyd et al., 2015) specifically excluded participants with mental retardation and suicidal ideation. Some exclusion criteria such as suicidal ideation should be given importance since suicidality is a potential adverse

event of DBS (Appleby et al., 2007), and people with AD are at an increased risk of committing suicide (Barak and Aizenberg, 2002). We recommend that the Neuropsychiatric Inventory should be used in all subsequent DBS for AD trials to exclude patients with depression and suicidal ideations (Cummings et al., 1994), and to monitor patients during and after the trial for the appearance of any depressive symptom or suicidal inclinations. Only one study has explicitly stated the use of the Neuropsychiatric Inventory in excluding patients with clinically significant psychiatric symptoms and as a clinical outcome measure (Lozano et al., 2016).

Since it has been suggested that those at an earlier AD stage and those who experienced in-surgery stimulation-induced autobiographical memories are more likely to benefit from fornix DBS (Laxton et al., 2010), determining which exact stage of AD are patients most responsive to fornix DBS and verifying if triggered autobiographical memories are indeed a good marker of eventual therapeutic response to DBS are crucial. In addition, since fornix DBS might have a potentially age-dependent effect (Lozano et al., 2016), it is important to determine whether age is indeed a true effect-modifying factor or if there is another underlying variable that happens to just be more prevalent in younger individuals with AD. As such, incorporating biomarker information such as hippocampal brain volume, CSF levels of tau and amyloid beta, and brain activity measured by EEG and fMRI (Lewczuk et al., 2015) in patient selection might provide more information on AD stage during recruitment and also on other variables that could influence a participant's response to DBS. Among the 3 trials, only one (Fontaine et al., 2013) provided evidence of potential AD pathology from CSF amyloid and tau levels.

Finally, it is important to consider AD's neurodegenerative nature and that most affected individuals are ≥65 (Hebert et al., 2013), and as such, participants could already have impaired decision-making capacity (Kim et al., 2001) that could compromise their ability to provide fully informed consent. Future trials should assess the ability of trial participants to consent using systematic or established measures of capacity assessment (Grisso et al., 1995; Marson et al., 1995), and from there, determine whether the participant's consent alone is enough or if additional consent from a caretaker or surrogate is needed. However, eventual support of caregivers might be necessary even for those who are fully competent at the start of the trial, and thus, their opinion might still have to be valued (Pierce, 2014). In addition, some participants might eventually lose adequate decision-making capacities, and as such, advance research directives should be made and surrogate decision makers/legally authorized representatives should be initially assigned to facilitate or guide decisions in later trial stages (Siegel et al., 2017). Among the trials, only one (Holroyd et al., 2015) required informed consent signed by the subject, a family caregiver, and a surrogate.

4.2. Trial design

An essential component of a DBS study is the stimulation parameters used given that they could impact the therapeutic effect of DBS (Cooper et al., 2008; Reich et al., 2015). Both phase I studies (Fontaine et al., 2013; Laxton et al., 2010) and the phase II trial (Holroyd et al., 2015) used a stimulation frequency similar to the one used in the study of fornix DBS to treat an obese patient (Hamani et al., 2008; Table 1). However, the phase I and phase II trials in North America (Holroyd et al., 2015; Laxton et al., 2010) both employed a longer pulse width than what was originally provided in the obese patient (Hamani et al., 2008). Given that the same research team facilitated these 3 studies in North America (Hamani et al., 2008; Laxton et al., 2010; Lozano et al., 2016), it would be important to determine the rationale behind increasing the pulse width. Interestingly, the phase I trial in France (Fontaine et al., 2013) employed an even longer pulse width but a relatively smaller voltage but did not really provide a rationalization for such deviation. Standardization is crucial and should be implemented in future trials to allow better compilation of results and to minimize potential variables that could influence experimental outcomes. Standardization should not be placed above patient welfare though, and adjustments, as long as they are accounted for and explained, should be made to minimize adverse events if they arise in certain participants.

The phase II trial of fornix DBS (Lozano et al., 2016) employs a design with a no-stimulation group for the first 12 months and then shifts to an open-label design where all participants will receive stimulation for an additional 12 months (Holroyd et al., 2015). It is interesting to compare this protocol with another trial of DBS targeting the nucleus basalis of Meynert in people with AD (Kuhn et al., 2015). This study consisted of an initial 1-month randomized double-blind sham-controlled stimulation phase, where 2 weeks of stimulation were followed by 2 weeks without stimulation or vice versa, with the 2 phases separated by a 24-hour washout period, and a succeeding 11-month phase of continued open stimulation on all participants. In the nucleus basalis of Meynert study, mean MMSE scores improved after 2 weeks of stimulation compared with the score after 2 weeks without stimulation. On the other hand, results from the phase II clinical trial (Lozano et al., 2016) showed no difference between the groups when analysis was performed just based on treatment arm, but accounting for age suggested variable effects of stimulation for different age groups (Table 1).

The differing set-ups of DBS for AD studies with controls (Kuhn et al., 2015; Lozano et al., 2016) raise the questions of how long should stimulation be withheld to be able to observe an adequate effect while ensuring that those who do not receive stimulation for a certain period are not dramatically disadvantaged, especially if DBS has the potential to improve participants' cognitive capacities only at a certain stage or period of impairment. Given the initial results of the phase I trial in Canada (Laxton et al., 2010), participants should be in a very mild stage of dementia in such a way that after 1 year without stimulation, they would not progress to a stage where they are unlikely to benefit from DBS. The 1-year report of the phase II trial (Lozano et al., 2016) did not analyze the influence of initial cognitive scores on therapeutic benefit, data on which might shed light on the participants with presurgery cognitive scores who are most likely to benefit from DBS. However, the phase II trial reported an effect of age, the results of which actually raise several concerns. Primarily, there was cognitive worsening in those <65, which appears to be much greater than the cognitive improvement in those ≥65. In addition, results of stimulation effect on CDR-SB were only significant for those <65. Such effect was in the negative direction though, suggesting that DBS might actually worsen cognitive decline in a certain subgroup of patients. This raises the issue of whether it might be ethical to continue stimulating participants <65 who are in the ON group and begin stimulation for those who were not initially stimulated (Viaña et al., 2017). Nonetheless, immediate conclusions that those <65 will be negatively affected by DBS might be unwarranted given that selecting 65 as a cut-off point has no biological significance and is mainly an indicative of social divide in terms of employment and retirement age (Rossor et al., 2010). Furthermore, no genetic tests or family background checks were mentioned in the phase II trial (Lozano et al., 2016) to determine if any of the participants have mutations that might lead to a more aggressive AD disease course (Ringman et al., 2014), which could affect outcomes and potentially explain the results for the younger patient subgroup (Viaña et al., 2017).

4.3. Outcome measures

All fornix DBS studies primarily aimed to determine the safety of the procedure, but all of them also examined its efficacy. All 3 trials

utilized ADAS-Cog, and each further utilized different additional cognitive and global measures ranging from MMSE, CDR, and FCSRT. All studies also performed cerebral functional examination via PET, and 2 studies (Holroyd et al., 2015; Laxton et al., 2010) measured hippocampal volume via MRI. As with stimulation parameters, the standardization of cognitive and neurologic tests is essential for better comparison of results from these studies. Moreover, having standardized cognitive and neurologic tests would help strengthen any evidence for the therapeutic effect of DBS and also simplify regulatory approval application processes.

Although the phase I trial report (Laxton et al., 2010) suggested potential memory improvements and increased temporal lobe metabolism and hippocampal volume from fornix DBS, it is important to note that half of the participants worsened after 3 months of stimulation, and after the 12-month period, 2 participants had worse performance than during the start of the therapy. In addition, the phase II trial (Lozano et al., 2016) showed significant cognitive worsening in stimulated participants <65 and only very mild improvement in those ≥ 65. Although these studies generally indicate that DBS of the fornix in people with AD is safe, its clinical significance should also be taken into account in making decisions on progressing to the next clinical trial phase where a larger participant cohort will be enrolled.

The benefits of stimulation of the fornix would be expected to have a particular time window that relates to the early involvement of the medial temporal lobe and hippocampus in degenerative changes with neuronal degeneration and the loss of axons, including those in the fornix. Although certain participants might expect immediate improvement of cognition, results in some subjects might only be witnessed after a longer period of stimulation (Laxton et al., 2010), despite the background of early degeneration of the hippocampal formation. This is in stark contrast with DBS for essential tremor and Parkinson's disease where patients see improvements in motor function shortly after the stimulation is started (Hristova et al., 2000). The possibility of late response highlights the importance of proper communication with people with AD about the possible time interval over which improvement could occur and that DBS might just stabilize cognitive status for a period of time rather than improve cognitive function.

It is also important to emphasize that several aspects of cognition, daily functioning, and social interaction are not well captured by common AD scales (Robert et al., 2010). In addition, although the various formal assessments of neurological function may help elucidate the mechanisms underlying potential memory improvements, they may not have much impact on trial participants when relayed to them. As such, cognitive and neurological changes should be related to functional outcomes, such as in activities of daily living and quality of life (QoL). In the Canadian phase I trial (Laxton et al., 2010), 4 out of 6 participants had improved scores in an AD-specific QoL scale. In the Clinician Interview-Based Impression of Change scale however, only 1 participant was reported to show improvement. Given that there are no controls for this trial, it would be difficult to attribute whether such improvement was due to the medication, surgical procedure, or the stimulation itself. Moreover, the 1-year report of the phase II trial (Lozano et al., 2016) did not really indicate what the results of the QoL-AD test are, although the inclusion of such test was initially indicated in their initial study description (Holroyd et al., 2015). In addition, scores of patients who received and did not receive stimulation in the AD Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL) did not differ; however, such was only the result when age is not accounted for. Given that the participants' age seemed to have an influence on the outcome of stimulation, ADCS-ADL results should have also been compared between the 2 age groups.

5. Conclusions

Results from animal studies could aid participant selection and trial design, yet current animal studies greatly differ in stimulation parameters and also use animal models that inadequately represent the underlying pathology of AD. These considerations highlight the need for collaboration among research centers and laboratories to establish standards in the stimulation parameters used and cognitive measures employed both in human and animal studies to facilitate better comparison of results and minimize confounding variables.

Preliminary results from small studies in humans indicate that fornix DBS in people with AD may be feasible and safe, although sufficiently powered larger studies are required. These and possible future studies bring up salient issues on appropriate participant selection criteria, framework for consent, and participant orientation procedure. There are also concerns relating to the design of subsequent clinical trials, particularly regarding the optimal AD stage for DBS intervention and the subgroups of people with AD that are most likely to benefit. Appropriate outcome measures need to be developed, particularly given outcomes may range from improvement in cognition from current levels, stability of symptoms, or continued decline. Obtaining a sufficiently powered study that addresses these issues of efficacy may prove challenging for such a surgical procedure given its highly invasive nature. In addition, the long-term safety of the surgery needs to be evaluated—very few studies have examined the pathological effects of placement of stimulating electrodes post mortem (Pilitsis et al., 2008; Sun et al., 2008). In this regard, the placement and activation of electrodes in axonal tracts that are already degenerating, such as the fornix in AD, may be an important consideration.

Economic, societal, and regulatory issues also have to be anticipated. An economic evaluation of DBS for mild AD suggests that in order for it to be more clinically and cost effective than standard care, it has to achieve an 80% success rate (Mirsaeedi-Farahani et al., 2015), a benchmark that results from past and ongoing fornix DBS for AD clinical trials seem to be relatively distant from. Even though DBS for AD would be close to or achieve such benchmark at some point, its widespread application would still be immensely challenging. Certain racial groups already have limited access to AD screening and standard treatment protocols (Dilworth-Anderson et al., 2012), in addition to restricted DBS for Parkinson's disease access and health care coverage for neurosurgical procedures (Chan et al., 2014). DBS also involves a complicated operation and requires a multidisciplinary team for monitoring, necessitating specialized psychiatric, neurological, and neurosurgical facilities and skillset, making its application in urban areas and developing countries with limited resources a big challenge. In addition, although certain people might have access to and health care coverage for DBS, they might be wary of and opt not to receive DBS treatment given that it could be a ground for rejection to nursing homes due to the increase in care needed (Farris and Gianola, 2009) and financial cost in the event of device-related complications. Regulatory challenges also have to be addressed, especially in attempting to use DBS in the context of treatment for people with AD (Schmitz-Luhn et al., 2012). Lessons have to be learned from the irresponsible marketing and use of "stem cells" for neurodegenerative conditions in connection with the alarming popularity increase of stem cell tourism (Jawad et al., 2012). Strict regulations and safeguards should be in place in different countries to prevent unregulated promotion and use of deep brain stimulation to "treat" people with Alzheimer's disease.

The burden of Alzheimer's disease is not just limited to the patient but extends to the family, caregivers, and society as a whole. In DBS for AD, this can be further complicated by the potential of DBS to affect social and family dynamics, as demonstrated in people

with Parkinson's disease that despite being relieved of motor symptoms through DBS, experienced self estrangement and/or post-operative changes in personality, outlook in life, and behavior that affected marital relations and professional activity (Agid et al., 2006; Gilbert, 2012). Although there are currently no reports on the effects of DBS on socio-familial dynamics for people with AD, these issues might potentially arise and have to eventually be reconciled with the effect of AD itself on familial relations, especially with communication difficulties and loss of affectional expression (Davies et al., 2010) and on how caregivers adapt and respond to it. Given the burden of AD and potential adverse effects of DBS to socio-familial dynamics, decisions on policies regarding access to and protocols for DBS trials and therapeutic application should involve and consider the needs and opinions of people with AD eligible for DBS and their families and caregivers.

Since there is no disease-modifying treatment available for AD, DBS might offer an additional mode of therapy. Nonetheless, sound and ethical scientific and clinical groundwork have to be established first before this highly invasive procedure that targets a vulnerable group of individuals is approved and recommended for wide use.

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Ethics Review

Ethical Considerations for Deep Brain Stimulation Trials in Patients with Early-Onset Alzheimer's Disease

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Abstract. Several studies of deep brain stimulation (DBS) of the fornix or the nucleus basalis of Meynert have been recently conducted in people with Alzheimer's disease, with several recruiting participants <65 and thus have early-onset Alzheimer's disease (EOAD). Although EOAD accounts for less than 5.5% of AD cases, ethical considerations must still be made when performing DBS trials including these participants since a portion of people with EOAD, especially those possessing autosomal-dominant mutations, have an atypical and more aggressive disease progression. These considerations include appropriate patient selection and signing of an informed consent for genetic testing; appropriate study design; potential outcomes that people with EOAD could expect; and accurate interpretation and balanced discussion of trial results. Finally, recommendations for future DBS for AD trials will be made to ensure that EOAD patients will not experience avoidable harms should they be enrolled in these experimental studies.

Keywords: Clinical trials as topic, deep brain stimulation, early onset Alzheimer's disease, ethical review, ethics, familial Alzheimer's disease, fornix (brain), nucleus basalis of Meynert

INTRODUCTION

There has been a recent surge in experimental trials on deep brain stimulation (DBS) for Alzheimer's disease (AD) [1–5], with several studies recruiting participants <65 [1, 3–5] and thus have early-onset Alzheimer's disease (EOAD). Although there have already been previous discussions on the ethics of DBS for neurodegenerative disorders [6–9], issues arising from recruiting people with EOAD for DBS trials remain unexamined and unexplored in the literature. To address this gap, we discuss potential ethical issues focusing on selection criteria, genetic testing and informed consent, study design, measured outcomes, and result interpretation and portrayal to protect people with EOAD participating in DBS for AD trials.

EARLY-ONSET ALZHEIMER'S DISEASE AND GENETIC PREDISPOSITION

Dementia affects an estimated 46.8 million people worldwide [10], with AD as its leading cause

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[11]. People with AD dementia suffer from cognitive or behavioral impairment in two or more domains, which include memory, reasoning and executive function, visuospatial abilities, language functions, and personality, that significantly interferes with ability to function at work or at usual activities [12].

Although the majority of people with AD are ≥65 [13], 5.5% of those affected have an onset of dementia before 65 [14] and thus are classified as having EOAD. The 65-year-old cut-off point has no biological significance and is mainly an indicative of social divide in terms of employment and retirement age [15]. Nonetheless, people with EOAD usually have a more rapid disease progression and have more pronounced brain pathology compared to those who develop AD symptoms after 65 [16]. In addition, they have a much shorter survival time; much more prevalent language disturbance [17]; exhibit other atypical symptoms such as visual agnosia, apraxia, dyscalculia, and executive dysfunction [18]; have a higher prevalence of additional non-cognitive neurological symptoms [19]; and exhibit more severe temporoparietal junction atrophy [20].

At least 62% of patients with EOAD have a history of AD in the family [21], implying potential genetic underpinnings. Currently, three genes have been fully established to cause highly penetrant and autosomal dominant AD: amyloid precursor protein (APP) and presenilin 1 and 2 (PSEN1 and PSEN2). PSEN1 makes up 30 to 70% of familial EOAD (EOFAD); followed by APP that accounts for 10–15% of EOFAD cases; and lastly, by PSEN2 that accounts for less than 5% of all EOFAD [22, 23]. Mutations in APP causes its aberrant processing and increased $A\beta_{42}$ secretion, whereas mutations in PSEN1 or PSEN2 lead to aberrant cleavage of APP by γ-secretase, resulting in an overproduction of $A\beta_{42}$ [16]. Overall, this leads to the biological cascade causing the observed cognitive defects in AD. The age of AD onset in PSEN1 mutation carriers is between 30 and 50 years old, 40 to 70 years in PSEN2, and 45 to 60 years in APP mutation carriers. Atypical presentations such as language impairment and behavioral symptoms such as delusion, hallucinations, and apathy have been observed in those with PSEN1 or PSEN2 mutations [22]. Certain APP mutations have also been linked to cases of congophilic angiopathy [23], which can lead to leukoencephalopathy, stroke-like episodes, hemorrhage, and cortical calcification [19].

Even though APP, PSEN1, and PSEN2 mutations are the only ones definitively proven to cause autosomal-dominant EOAD, the presence of an APOE ε4 allele has also been associated as a risk factor for typical AD and potentially reduces its age of onset by roughly 10 years. It is not a necessary component though since patients who typically exhibit an atypical and early-onset AD course, exhibiting focal cortical, non-memory impairments, and a more aggressive progression, can develop AD even in the absence of an APOE ε4 allele [18]. Nonetheless, patients who have APP, PSEN1, or PSEN2 mutations could also have a much earlier age of onset if they possess an APOE ε4 allele [23, 24].

Currently, people diagnosed with EOAD are given the same treatment as those who have late-onset Alzheimer's disease (LOAD), given similarities in pathogenesis and clinical features [19]. Only six drugs are FDA-approved for the management of AD symptoms; however, none of them stops disease progression [25], treats the underlying pathology, or provides long-term benefit [26]. As such, several clinical trials on different modes of treatment are being undertaken to either provide additional long-lasting relief from symptoms or treat the underlying AD neuropathology. Among the treatment modalities being investigated is DBS, a procedure wherein leads are inserted into the brain region of interest to deliver continuous electrical stimulation [27], with the hope of ameliorating cognitive dysfunction. Currently, DBS has regulatory approval for essential tremor, Parkinson's disease, dystonia, obsessive-compulsive disorder, and epilepsy [28].

CLINICAL STUDIES ON DEEP BRAIN STIMULATION FOR AD

The first experimental trial on DBS for AD was performed in 1984 where the nucleus basalis of Meynert (NBM) was stimulated. Although there was no improvement in memory or cognition, preserved cortical glucose metabolic activity in the left parietal and left temporal lobes and partial arrest of deterioration in the left frontal area were observed [29]. The next clinical trial was performed 26 years later [1], and it was driven by a serendipitous discovery in 2008 when DBS of the fornix to treat obesity resulted to "deja vu-like" sensations during surgery and improvements in episodic verbal and associative memory after three weeks of stimulation [30]. The 2010 Phase I trial investigated DBS of the fornix in six patients with early AD. Similar to the 2008 study, two patients experienced autobiographical experiential phenomena during surgery. In addition, after

12 months of continuous DBS, some patients were reported to have improved memory and reduced cognitive decline, reversed glucose metabolism [1], and increased hippocampal volume [31]. Given that the Phase I trial was considered to have proven the safety of DBS of the fornix and showed metabolic changes associated with it, a Phase II randomized, double-blind, placebo-controlled, delayed-start trial is currently being conducted in 42 subjects with mild, probable AD. In this trial, half of the subjects will not receive any stimulation while the other half will receive continuous DBS stimulation for 12 months; after which, all participants will receive stimulation for 12 months [32]. Results of the first year of this trial have already been published and indicate no significant difference in cognitive scores between those who received and those who did not receive stimulation. However, stratifying participants based on age showed that those who are <65 actually significantly worsened after DBS for one year, whereas those ≥65 had a slight improvement in cognitive function. In terms of safety, there were 145 and 117 non-serious adverse events in patients that received and did not receive stimulation, respectively. In addition, nine serious adverse events for each participant subgroup were reported. Serious adverse events include those that lead to prolonged hospital stay, new hospital admission, disability, or death, such as infection, lead repositioning, post-op nausea, depression, suicidal ideation, and worsening confusion. Non-serious adverse events are predominantly general medical in nature, followed by psychiatric events. Taking into account the nature and extent of reported adverse events, an independent data and safety monitoring board concluded that the observed safety profile was as expected with deep brain stimulation [3].

Aside from the aforementioned Phase I [1] and Phase II trials [3] of fornix DBS in North America, several other case studies and trials of DBS for patients with AD have been reported. A team in France performed fornix DBS in a patient with mild cognitive decline. After 12 months of stimulation, the patient's cognitive performance reportedly stabilized, and the patient also had increased mesial temporal lobe metabolism [2]. Aside from the study done in 1984 [29], another trial of DBS of the NBM was also performed by Kuhn et al. [4] where six patients with mild to moderate AD received bilateral DBS. Their study consisted of an initial one-month randomized sham-controlled stimulation phase, where two weeks of stimulation was followed by two weeks without stimulation or vice versa, and a succeeding 11-month phase of continued open stimulation on all patients. During the first month, mean Mini-Mental State Examination (MMSE) scores improved after two-weeks of stimulation compared to the score after two weeks without stimulation. After almost a year of stimulation, cognitive assessments revealed slower disease progression when compared to patients undergoing medication. In addition, some patients exhibited increased temporal and amygdalo-hippocampal glucose metabolism after almost a year of stimulation. In terms of safety, the surgical procedures were well tolerated, and the patients had fast recovery and did not have significant stimulation-induced untoward effects [4]. Kuhn et al. [5] then further extended their study and performed continuous DBS of the NBM in two patients who have an average age younger than the average of those in the Phase I trial and who both have lower baseline ADAS-Cog scores. One participant deteriorated after 26 months based on ADAS-Cog and MMSE scores, whereas the other participant had a stable ADAS-Cog and even improved MMSE score after 28 months. Hardenacke et al. [33] then collated the results of the Phase I trial [4] and that of the two new patients [5] and suggested that NBM-DBS performed at a younger age and at an earlier disease stage may favorably impact cognitive functions and disease progression.

ETHICAL CONSIDERATIONS ON DBS STUDIES ON PEOPLE WITH EOAD

Majority of the trials [1, 2, 4, 32] performed or currently ongoing recruited patients who are less than 65 years old, and thus could potentially have EOAD. Given that DBS is an invasive procedure that could lead to a number of neurologic and psychiatric unwanted side effects [34], it is important to consider ethical issues that may arise when performing it to different patient subgroups, especially to individuals less than 65 who might have certain mutations that could lead to a more aggressive disease course [16].

Considerations for patient selection

Four out of six reported studies [1, 2, 4, 32] posted recruitment details on the clinicaltrials.gov database and described them in their papers (Table 1). From this information, it is evident that five out of six DBS for AD studies recruited a total of 19 participants <65, all of which have at least mild cognitive impairment. This indicates an overrepresentation of EOAD in the study population (32.7%) given that

Table 1
Criteria for patient recruitment in studies on DBS for AD and number of recruited participants who are less than 65

Study	Region	N<65	Age	AD stage	Cognitive score	Biomarker	Suicidality	Informed consent
Turnbull et al. [29]	NBM	0/1			No mention			
Laxton et al. [1]	fornix	5/6	40–80	Probable AD (1983 NINCDS-ADRDA)	CDR of 0.5–1, MMSE of 18–28	–	–	Patient or surrogate
Fontaine et al. [2]	fornix	0/1	50–70	AD DSM IV	Episodic memory impairment from FCSRT/ Grober and Buschke test; MMSE of 20 to 24	MRI and/or CSF and/or PET proposed to patient	–	Patients
Kuhn et al. [4]	NBM	1/6	57–80	Mild to moderate AD – DSMIV, ICD10, NINCDS-ADRDA	MMSE >18, <26	CSF tau and $A\beta_{42}$	Suicidal tendency	Patients and at least 2 family members
Kuhn et al. [5]	NBM	1/2			No mention			
Holroyd et al. [32]; Lozano et al. [3]	fornix	12/42	45–85	Probable AD (2012 NIA-AA)	CDR of 0.5 to 1; ADAS-Cog 11 of 12–24, score ≥4 on Item 1: immediate recall	–	Suicide past 2 years; C-SSRS	Subject, caregiver, and surrogate

NBM, nucleus basalis of Meynert; NINDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA); DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD10, World Health Organization International Statistical Classification of Diseases and Related Health Problems; NIA-AA, National Institute on Aging-Alzheimer's Association; CDR, Clinical Dementia Rating scale; MMSE, Mini-Mental State Exam; FCSRT, Free and Cued Selective Reminding Test; ADAS-Cog 11, Alzheimer's Disease Assessment Scale – cognitive component; C-SSRS, Columbia Suicide Severity Rating Scale; CSF, cerebrospinal fluid.

only around 5.5% of people with AD have an early disease onset [14]. Such overrepresentation of EOAD patients might not have been deliberately made by the authors and could have just been a result of better success in recruiting and enrolling younger patients due to their greater capacity to tolerate surgery [35] and provide consent [36]. Furthermore, these studies did not mention performing any family background checks or genetic tests for APP, PSEN1, and PSEN2, which makes it possible that a participant enrolled could also have familial (EOFAD) or autosomal-dominant EOAD (AD-EOAD). If one considers that the proportion of autosomal dominant EOAD patients among all EOAD patients is 13% [21], then it seems likely that at least two patients (13% of 18 = 2.34) with AD-EOAD have already participated in these trials. Interestingly, patient 3 in the Phase I trial of Laxton et al. [1] was below 65, had an aggressive disease course prior to surgery based on MMSE scores, and had the worst outcome post-DBS based on MMSE scores. As such, patient 3 might actually have a form of EOFAD or AD-EOAD; however, this cannot be ascertained given that no family background checks or genetic tests were presented in the report. Considering that people <65 are being recruited in DBS for AD studies, we suggest considerations and adjustments in certain inclusion and exclusion criteria when patients with EOAD are potentially recruited in studies, especially those who have autosomal-dominant EOAD.

First, since certain AD-EOAD patients could exhibit atypical behavioral symptoms and DBS could have unwanted psychiatric effects [34], recruited EOAD patients should not have any major psychiatric disorder, especially those that increase the risk of suicide, such as depression, schizophrenia, and substance use disorders [37, 38]. Participants with a history of and/or who were experiencing suicidal ideations at the time of recruitment should be excluded in trials considering that suicidality is a potential adverse event of DBS [39–41]; patients with AD have an increased risk of committing suicide [42]; and people with certain autosomal AD mutations have a high risk of depression and disinhibition [43]. Of all the studies of DBS for AD, only two studies [4, 32] specifically excluded patients who had previous suicide attempts or who have suicidal ideations. Moreover, should appropriate consent be given to employ genetic testing in patients with a family history of AD, careful counselling should be provided to minimize the risks of increased suicidal ideation from an untoward result. Proper tests and monitoring should then be made to ensure that individuals with positive results do not exhibit any suicidal tendencies or ideations prior to commencing DBS surgery.

Second, potential adjustments in the required cognitive profile and disease stage of recruited EOAD patients should be made to account for its shorter disease duration and more aggressive course, especially in participants who have autosomal-dominant mutations [22]. In past and ongoing studies of DBS for AD, some trials [1, 2, 32] only recruited patients with mild AD, whereas Kuhn et al. [4] also included those with moderate AD. In terms of cognitive profile, two studies [1, 32] recruited patients with a Clinical Dementia Rating (CDR) of up to 1, two studies [1, 4] recruited patients with MMSE as low as 18, and one study [32] recruited patients that have an ADAS-Cog 11 score as high as 26. The inclusion of patients with CDR, MMSE, and ADS-Cog 11 scores that already signify cognitive decline beyond the mild cognitive impairment stage [44] and at the start of the dementia phase warrants serious consideration when patients with EOAD are included in a study, given EOAD's more aggressive disease course [16]. Considering the initial results of Laxton et al. [1] and Hardenacke et al. [33] showing that patients in an earlier disease stage are more likely to benefit from DBS, there is a need to modify the cognitive status cut-offs for participants <65 participating in DBS for EOAD studies. EOAD patients that have a CDR score >0.5, MMSE score <23, and ADAS-Cog 11 score >18 [45], and possess mutations predisposing them to more aggressive cognitive deterioration [22, 23] should not be included in DBS studies unless more evidence has been gathered regarding the efficacy of DBS in later AD stages. Although the use of most biomarker data as diagnostic tools has not yet been approved clinically, hippocampal volume, tau, and Aβ cerebrospinal fluid levels, and brain activity [46] could also be used in conjunction with cognitive tests to ensure that enrolled EOAD patients are at an early disease stage.

Third, it is important to consider the effect of excluding or only including certain patient subgroups based on participants' cognitive, genetic, and/or biomarker profile on the study's external and internal validity and also to determine whether it violates the clinical responsibility to provide patients access to certain treatments [47]. Excluding participants with EOAD or including only EOAD participants might increase a study's internal validity due to increased subject homogeneity; however, such could also consequently diminish a study's external validity [48, 49]. Although preliminary trials on drugs and certain

interventions are often done on more homogeneous populations as a result of relatively narrow selection criteria [50], participant recruitment for invasive neurosurgical procedures such as DBS could be extremely challenging, especially when highly stringent selection criteria are employed [2]. As such, recruiting an immensely homogeneous sample might not be possible in the context of preliminary DBS trials. Furthermore, trials including different populations for invasive procedures could provide better knowledge of different subpopulations that could be more responsive to treatments, provided that no subpopulation is significantly disadvantaged or harmed by the intervention in accordance with the ethics principle of Nonmaleficence [7, 51]. However, since initial results from the Phase II fornix DBS trials suggest that participants <65 could worsen from DBS [3], excluding them from subsequent fornix DBS trials, especially those with moderate AD, might be warranted until subsequent in-depth analyses have been made to ascertain if age is indeed the sole causative factor associated with the observed decline or if other variables such as genetic and cognitive status actually better explain the variable effects of treatment between different patient subgroups. This further emphasizes the importance of obtaining additional information on genetic status and biomarker information in participants so that those who are either likely to benefit or are likely to be harmed by DBS would be better and more precisely identified. Given that DBS for AD has not been approved yet by an established regulatory body (e.g., FDA) as a standard of care and its application is still in the context of clinical trials, denying access to it for certain patient subgroups could not be considered as denial of treatment.

Genetic vulnerability and informed consent

Since the corresponding clinical progression resulting from certain AD-associated mutations has already been recorded [23], making the correct adjustments such as allowable time period to withhold treatment and frequency of monitoring for patients with certain EOAD genetic subtypes would be much better facilitated if detailed genetic information is available. However, requiring genetic testing for autosomal dominant AD mutations in all or certain trial participants raises its own set of ethical issues, requires adjustments to the informed consent process, and entails additional procedures that have to be included in the trial (Fig. 1).

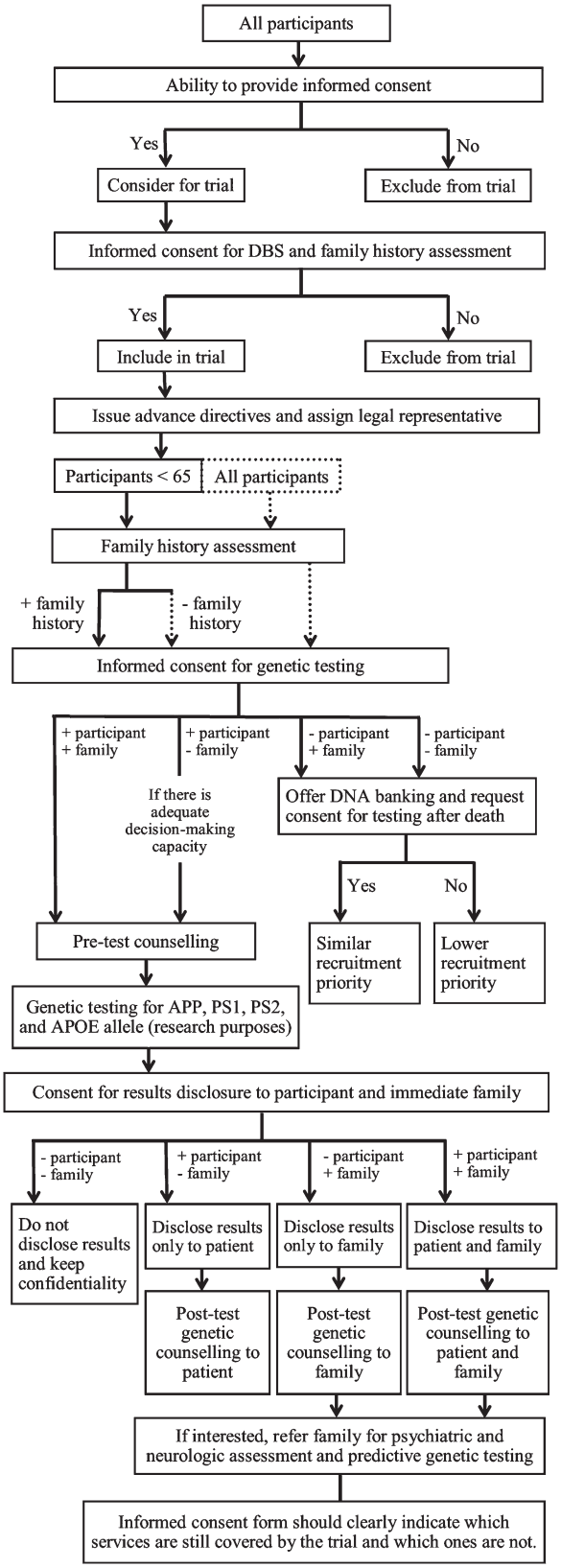

Fig. 1. Decision tree for providing informed consent and for genetic testing in DBS trials including people with early-onset Alzheimer's disease. Solid boxes, lines, and arrows indicate suggestions that must be minimally fulfilled. Dashed boxes, lines, and arrows indicate optimum suggestions.

First and foremost, even before having participants sign an informed consent form, it is important for all studies to assess their ability to consent using systematic or established measures of capacity [52, 53]. Participants who do not fully understand the risks of the invasive neurosurgical procedure or the associated uncertainty to benefit from the trial, given the limited data from preliminary studies, should be excluded.

Second, should genetic testing be required, it should be specified in the informed consent form that participants will consent to the DBS surgery and stimulation and all other pre- and post-clinical testing, including genotyping of APP, PSEN1, PSEN2, and/or APOE. The genotyping that will be performed should be clearly indicated. Both patients and immediate family members should be given options to decide whether they would like to have the results of the genetic tests disclosed or not. Since approved prevention methods [54] and treatment options for AD do not exist yet, there is no obligation for deliberate disclosure of genetic test results to participants and immediate family members [55]. Nonetheless, pre-disclosure genetic counselling using established guidelines [56, 57] should be provided to both patients and immediate family members to allow them to better understand the implications of results disclosure [58, 59], particularly on reproductive [60], insurance [61], and geriatric care planning and also on potentially being able to access certain clinical trials for those with autosomal dominant AD [62]. Should patients and/or immediate family members prefer to know results, further support in the form of post-disclosure genetic counselling sessions could be provided [57]. It should be emphasized that the risk of inheriting a mutation from a parent with autosomal dominant AD is 50%, and immediate family members who wish to undergo predictive genetic testing themselves should be referred to a genetic counsellor, neurologist, and psychologist/psychiatrist for further evaluation and support [56, 63]. Consequently, since payment for further testing and counselling sessions would raise financial concerns [64] for those conducting the trial and/or those participating in it, the extent of genetic counselling and compensation that will be provided should be clearly indicated in the informed consent form [51] to better allow family members to decide on whether they would still prefer to be informed of the results and understand potential limitations in the support that they would be receiving in the event of an unfavorable result. Finally, patients who do not consent to genetic testing should not be directly excluded from trials and should be offered alternative options such as family history assessment [65] for autosomal dominant EOAD risk estimation and DNA banking [56] for potential genetic testing after the patient's death [66], with his or her consent. Those who do not consent to such alternatives might be given lower priority to participate in a trial.

Third, since a significant number of studies of DBS for AD [4, 32] required the consent of family members or caregivers, requiring genetic testing could raise potential issues when the patient but not the family members would consent to participation in the trial and consequentially, genetic testing [55]. Although at the start of the trial, participants with EOAD at a very early disease stage might still have adequate ability to consent, they might eventually need a caregiver when the disease rapidly progresses, and as such, caregivers' opinions and support on a patient's participation in a DBS trial [8] would be of increasing importance in later trial stages. This highlights a potential dilemma when there are conflicting opinions. The final decision on whether a participant should participate in a DBS trial and have a genetic test should then be made only after having a careful and collaborative discussion with the researchers, clinicians, family members, and the participant. If there are still conflicting opinions after the deliberation, we recommend that the decision of participants who have adequate decision-making capacity at the start of the trial be honored. Should the participant want to undergo DBS and genetic testing, legal representatives and advance research directives [7] should also be determined and set by the participant prior to DBS implantation. Given that several states and countries only allow consent on the subject's behalf when the patient has a legal status of incompetence [67], legal representatives might have to make eventual decisions on whether to continue DBS stimulation; however, there might be a point prior to complete incompetence when the capacity to consent is uncertain and solely obtaining consent from caregivers would not be the best option from an ethical perspective [68]. In such instances, researchers could also seek assent from participants and exclude those expressing dissent [7], which may be indicated by signs or actions of frustration, unhappiness, discomfort, or passivity [69].

Disease progression and study design

Only two trials [4, 32] of DBS for AD have a case-control design, albeit with different durations in which stimulation was withheld from the control

group. Withholding DBS for a long time from participants with EOAD might not be justifiable considering that DBS is an invasive procedure with potential unwanted side effects [34, 70, 71], and people with EOAD might have a more aggressive disease course and higher mortality than LOAD [72]. It should also be taken into account that although the Phase I trial showed that patients who had milder cognitive symptoms at the time of DBS initiation have seemingly better metabolic and cognitive outcomes [1], the Phase II trial indicated in its subgroup analysis that participants <65 actually had worse cognitive scores after stimulation for one year, whereas the opposite was observed for those ≥65 [3]. Since results for each individual participant <65 were not presented, it is not yet known whether all of them experienced decline after DBS or if it is only a few with other characteristics such as lower cognitive profile or more advanced disease stage. In addition, it would be interesting to know if combining the results for the five participants <65 in the Phase I fornix DBS trial [1] with the results for those <65 in the Phase II trial [3] would still lead to the same observed differential effect of DBS for this subgroup. Given such uncertainty, it might be possible that some participants <65 could have also benefitted from the stimulation given that some participants <65 in the Phase I trial [1] had stabilized or improved cognitive scores following DBS. For those <65 who might benefit from stimulation and for the rest of participants who were in the control group, withholding stimulation for a year could potentially result to a loss of a significant number of time and treatment opportunities where their cognition could still be stabilized. Although patients will continue receiving medications for memory during the period without stimulation, limiting them from attaining any eventual potential benefit from the surgery and even potentially causing them harm should any untoward incident result from surgery or stimulation would be unfair. On the other hand, for those <65 wherein stimulation could be disadvantageous, having a shorter stimulation time instead of one year could have potentially allowed initial detection of the stimulation's potential adverse effect, and appropriate actions could have been taken to prevent further harm in these patients.

The initial results of the Phase II trial also bring into question whether the study design has to be modified given that those <65 might be disadvantaged. It is important for Lozano et al. [3] to look at individual patients who deteriorated the most in the <65 stimulation group and see whether stimulation might need to be stopped for them instead of allowing them to continue to the one year open stimulation phase. In addition, those who are <65 who were originally assigned to the control group and have similar cognitive profiles as those who were most severely disadvantaged by DBS might not need to participate in the trial's next phase and not receive any stimulation given that these participants might actually be harmed by it. Although these adjustments to the study design could have some effect on the study's power if ever implemented, it is more important to protect participants' welfare, especially if there is convincing evidence that their further participation could lead to avoidable harms.

In terms of patient monitoring, studies usually monitored performance in various cognitive and neuropsychiatric tasks a month, three months, six months, and a year after surgery. However, when participants with a potentially more rapid disease progression are included [23], more frequent monitoring (bimonthly or monthly) should be implemented. Given that those <65 who received stimulation for one year in the Phase II trial had worse outcomes than those who did not [3], much more frequent monitoring would have allowed the initial detection of this potential worsening and would have allowed more data to be obtained to determine the rate of disease progression and compare it with that prior to stimulation or with historical controls. Moreover, given that some people with AD-EOAD experience atypical symptoms [19] such as behavioral impairment, apraxia, and aphasia, stringent examination and careful neuropsychiatric monitoring before and post-implantation should be made to ensure that any neuropsychiatric or motor attributes would not be affected in a way that is detrimental to the patient.

Potential trial outcomes

All the trials that have been completed [1, 2, 4] and the Phase II trial [32] that is ongoing assessed the efficacy of DBS using a cognitive test (MMSE, ADAS-Cog, CDR, FCSRT); however, several studies have also employed measurements of metabolism via PET [1, 2, 4, 29, 32], brain activity through EEG [4], and changes in hippocampal volume through MRI [1, 32]. Some studies also assessed the participant's quality of life [1, 4, 32]. For the Phase I studies [3, 5], results on the quality of life have been inconsistent with an increase in some participants and a decrease in others. For the Phase II trial, Holroyd et al. [32]

mentioned that they will be including the Quality of Life – Alzheimer Disease measure [73]; however, Lozano et al. [3] did not mention the result of this test in the report they have published [9]. All studies have also reported improved or preserved neurologic activity in certain brain areas; however, the translatability of these improvements to the trial participants' quality of life and daily functioning has yet to be adequately proven.

Although in general, the final pathophysiology in EOAD and LOAD may be greatly similar, the initial disease progression and onset of EOAD and LOAD might have some differences that could lead to potentially variable outcomes during early disease stages. For instance, EOAD patients have more pronounced atrophy in neocortical areas as opposed to LOAD patients wherein atrophy is more severe in the hippocampus [74]. Moreover, EOFAD patients also present with apraxia, aphasia, or dysexecutive syndrome [19]. As such, additional modes of assessment should be performed in studies involving patients with EOAD to determine how DBS affects these cognitive domains and motor symptoms. It might also be possible that EOAD patients might have a different initial clinical outcome given that degeneration usually is not as prominent in the hippocampus. Depending on the target region for DBS, the extent of changes or duration of stabilization in cognitive scores could differ between EOAD and LOAD patients. Although the results of the Phase II trial might indicate that fornix DBS could potentially be disadvantageous for those <65 [3], such might not necessarily be the case for NBM stimulation. Given these, it is important to properly convey these potential sources of differential DBS response to EOAD patients, especially those with family history and mutation in APP, PSEN1, or PSEN2, so that they will be more informed when they consent to the procedure and also to increase the likelihood that they will monitor the effects of stimulation on these atypical symptoms once the trial has been initiated.

Interpretation and communication of study results

Results of preliminary studies are used to plan the next stages of clinical trials [75]; however, they should not be used to justify efficacy and safety [75, 76] in a clinical setting. It is important that trials should convey this in their discussion and conclusion to prevent creating false hype. In addition, they should also highlight limitations in their methodology that could have affected study results. For example, Kuhn et al. [4] mentioned that it proved impossible for them to precisely insert the electrode in their preselected target due to degenerative or pathological vascular alterations. Although they mentioned this as a limitation of their study, they should have reflected more on whether this limitation would then make precise targeting of a desired region in the NBM totally not feasible instead of just concluding that DBS of the NBM is "technically feasible". In addition, they also mentioned that NBM DBS "apparently lacks significant stimulation-induced untoward effects"; however, they mentioned that one patient required lorazepam during the stimulation phase without fully describing why and at which exact points during the open stimulation phase was the drug prescribed. Finally, it is important to emphasize that the conclusion that DBS is "well tolerated" and that "four out of six patients were responders" should only be considered in the context of deciding whether to do a subsequent clinical trial in a proper and well-regulated research setting and not allowing for NBM DBS to be performed on anyone with AD in a clinical setting given that the study's limited sample size is inadequate to capture a wide range of potential adverse events and derive any statistically valid conclusion on the efficacy of DBS.

Another important aspect in reports of trials is for authors to completely report the results of all statistical tests that they perform. In the results of the Phase II trial [3], the observed difference in results between those who received stimulation and those who did not is much more dramatic for those <65, whereas only slight improvements in cognitive function were observed for those who are ≥65. Although the authors mentioned the result of the statistical tests for the <65 group, they did not provide p values for the ≥65 group for readers to determine the significance of the observed decline between those who received and those who did not receive stimulation.

Finally, it is important to consider that the 65 years cut-off point has no biological significance and is mainly based on employment and retirement age [15]. As such, it is crucial that further analysis for the Phase II trial [3] should be performed based on other factors such as disease stage, cognitive scores at the start of the trial, and/or extent of AD pathology based on biomarkers such as brain volume and levels of tau and/or Aβ in the cerebrospinal fluid [9,

46]. In addition, relating genetic data to treatment outcomes could potentially allow for better explanation of results obtained for those <65. It is possible that those who were made worse off by DBS have genetic mutations that result to a more aggressive disease course [16], and these individuals are also at a later disease stage at the trial onset. Reporting effects for participants having known mutations might require presentation of individual de-identified data to facilitate comparison of the rates of progression for individuals possessing mutations in known genes and accurately determine if DBS might have affected the rate of disease progression for these participants. Although introducing other variables in the analysis would add another level of complexity, they could facilitate improved understanding of the factors that affect DBS response, allowing better selection of suitable participants in future trials. Caution should be exercised in drawing conclusions though given that analysis based on subgroups usually lacks adequate power and may yield false-negative results, unless the initial trial power calculation significantly accounted for eventual subgroup analysis [77].

CONCLUDING REMARKS AND FUTURE CONSIDERATIONS

Studies that conducted DBS in patients with AD have not screened patients less than 65 years old for a family history of EOAD; mutations in APP, PSEN1, or PSEN2; or have APOE alleles that could affect age of disease onset and potentially, rate of progression [78]. As such, participants who have a familial or genetic AD that have a more aggressive disease course might have been disadvantaged by trials in terms of the employed study design and frequency of monitoring.

Although we believe that larger studies on DBS for EOAD should only be conducted after an extensive positive appraisal of the long-term results of the ongoing Phase II trial taking into account previous trials and relevant animal studies, we would like to propose certain precautionary recommendations for potential trials in the future that would include participants <65 (Table 2). First, in terms of patient selection, EOAD patients who have psychiatric disorders, suicidal ideations, and who are

Table 2
Recommendations for DBS clinical trials, especially those involving participants with EOAD, based on gaps in current and previous trials and case studies

Clinical Trial Aspect	Recommendations
Participant Selection	• Exclude participants who have a major psychiatric disorder, suicide history, and suicidal ideations. • Exclude participants beyond the mild cognitive impairment/ very mild AD stage (CDR score >0.5, MMSE score <23, and ADAS-Cog 11 score >18). • Use potential biomarker information to better estimate disease stage.
Genetic Testing	• Test for mutations in APP, PS1, and PS2, and if possible, determine APOE alleles possessed (for research purposes). • Provide pre-test and post-disclosure genetic counselling to participants and their immediate family.
Informed Consent	• Assess ability to consent using established measures of capacity. • Request consent both for DBS and genetic testing. • Offer alternative options such as DNA banking for those who do not wish to undergo genetic testing. • Clearly indicate what counselling and predictive genetic testing will be performed and which services are covered by the trial organizers. • Collaborative decision making should be made in case of conflicting opinions; however, a participant's decision should be honored if he or she has adequate capacity to consent. • Assign legal representatives and advance directives for participants. • Incorporate patient assent and dissent in decision-making in later trial stages.
Trial Design	• Initially assign a shorter stimulation period (<1 year). • Stimulation might have to be discontinued in the event of evident cognitive decline from DBS. • Monitor participants more frequently (monthly or bimonthly) and include assessments for atypical symptoms in people with EOAD and for neuropsychiatric changes.
Outcome Measures	• Include quality of life measurements in trials and report their results in publications. • Include additional modes of assessment for atypical symptoms in people with EOAD. • Acknowledge potentially variable outcomes between EOAD and LOAD participants and possibly different effects of fornix and NBM DBS on different patient subgroups.
Reporting of Results	• Realistically convey whether certain methodological limitations affect feasibility of DBS for particular regions. • Provide more specific details of adverse events and how they were addressed. • Completely report results of all statistical tests. • Analyze other variables that could result to different responses to DBS such as disease stage and genetic status.

already at the dementia phase should be excluded in studies until results suggest that DBS might also be effective in later AD stages. Second, genetic screening of patients <65 years old should be included in trials; however, disclosure of results has to be discussed with patients and relatives. Third, appropriate adjustments on the length of exposure to trial arms, assessments performed, and frequency of monitoring should be made to accommodate differences in EOAD and LOAD should people <65 be included. Fourth, study results should be realistically conveyed and should be reported equally regardless of the direction of the effect. Researchers and the media should be careful not to hype up results of preliminary studies to ensure that EOAD patients volunteering to enroll in an experimental trial are fully informed and not just misled by overly positive depictions of DBS for AD [79]. Finally and most importantly, collaboration between basic researchers, neurologists, psychiatrists, neurosurgeons, genetic counsellors, ethicists, and other aged care personnel should be established to set a proper framework ensuring that patients with EOAD are appropriately prepared and informed, well-protected, unharmed, and are not deprived of potential therapeutic benefits in future clinical trials of DBS for AD.

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Deep brain stimulation for people with Alzheimer's disease: Anticipating potential effects on the tripartite self

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Abstract

Memory dysfunction and cognitive impairments due to Alzheimer's disease can affect the selfhood and identity of afflicted individuals, causing distress to both people with Alzheimer's disease and their caregivers. Recently, a number of case studies and clinical trials have been conducted to determine the potential of deep brain stimulation as a therapeutic modality for people with Alzheimer's disease. Some of these studies have shown that deep brain stimulation could induce flashbacks and stabilize or even improve memory. However, deep brain stimulation itself has also been attributed as a potential threat to identity and selfhood, especially when procedure-related adverse events arise. We anticipate potential effects of deep brain stimulation for people with Alzheimer's disease on selfhood, reconciling information from medical reports, psychological, and sociological investigations on the impacts of deep brain stimulation or Alzheimer's disease on selfhood. A tripartite model of the self that extends the scope of Rom Harré's and Steve Sabat's social constructionist framework was used. In this

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model, potential effects of deep brain stimulation for Alzheimer's disease on Self 1 or singularity through use of first-person indexicals, and gestures of self-reference, attribution, and recognition; Self 2 or past and present attributes, knowledge of these characteristics, and continuity of narrative identity; and Self 3 or the relational and social self are explored. The ethical implications of potential effects of deep brain stimulation for Alzheimer's disease on the tripartite self are then highlighted, focusing on adapting informed consent procedures and care provided throughout the trial to account for both positive and negative plausible effects on Self 1, Self 2, and Self 3.

Keywords
Alzheimer's disease, deep brain stimulation, memory, cognition, selfhood, identity

Introduction

Alzheimer's disease (AD) affects at least 28 million people worldwide (Alzheimer's Association, 2015), causing significant impairments in memory, reasoning and executive function, visuospatial abilities, language functions, and/or personality (McKhann et al., 2011), in addition to significant emotional and physical burden to caregivers (Wright, Doherty, & Dumas, 2009). With these, AD could influence the identity and selfhood of affected individuals, both from their perspective and that of their family or caregivers (Caddell & Clare, 2010). Currently, there is a surge in using deep brain stimulation (DBS), a procedure that implants leads in the brain and a pulse generator in the chest to provide electrical stimulation to a brain region of interest (Okun, 2012), to target symptoms of AD (Fontaine et al., 2013; Kuhn et al., 2015; Laxton et al., 2010; Lozano et al., 2016). Initial trial results suggest that DBS is safe and might have some positive effect on cognition and memory for certain people with AD (Fontaine et al., 2013; Kuhn et al., 2015; Laxton et al., 2010; Lozano et al., 2016), which could potentially restore altered selves due to the disease. However, DBS itself has been associated with postoperative personality and psychiatric changes (Appleby, Duggan, Regenberg, & Rabins, 2007; Gilbert, 2012, 2013; Gilbert, Goddard, Viaña, Carter, & Horne, 2017), which could also influence a recipient's selfhood and identity.

Although there are a number of papers that have already explored the ethics of the use of DBS in people diagnosed with AD (Ovadia & Bottini, 2015; Pierce, 2014; Siegel, Barrett, & Bhati, 2017; Viaña, Bittlinger, & Gilbert, 2017; Viaña, Vickers, Cook, & Gilbert, 2017), none has extensively investigated issues arising from its potential effect on selfhood and identity, relating it to how AD already affects these aspects. Given this gap in the literature, we explore the potential effects of DBS on the selfhood of people with AD and their associated ethical implications using an extended version of the social constructionist model (Harré, 1991; Sabat & Collins, 1999; Sabat & Harré, 1992), which incorporates non-verbal components of selfhood and identity. In this revised tripartite self model, Self 1 encompasses self recognition, referencing, and attribution; Self 2 includes physical and mental attributes, self-knowledge, and consistency of self narratives; and Self 3 refers to social aspects of selfhood, focusing on relational aspects and social positioning.

Search strategy

References included in this article were obtained through a search on PubMed, Scopus, and Google Scholar until 11 September 2017 using the keywords "Alzheimer's disease", "dementia", "deep brain stimulation", "selfhood", "social constructionist", and "identity" and their corresponding permutations and combinations. The references of highly relevant articles were also examined to expand the search coverage and identify other articles related to the initial keywords used. Primary studies and case reports that explored the impact of AD on the social constructionist framework's three aspects of the self were identified and highlighted in this review. There were no studies that investigated the impact of DBS on selfhood using the social constructionist framework, so relevant studies that discussed its effects on self recognition and perception, psychological and psychiatric profiles, identity, and social adjustment were referenced instead. Results from clinical trials of DBS in people with AD were also obtained using this search strategy, mainly through the keyword "DBS Alzheimer's disease". No specific period was set during the searches, and only articles that are fully in or with abstracts in English (for a cited case report in Dutch) were included in this manuscript.

AD and the self

Studies on the effect of AD on selfhood have mostly used the social constructionist model (Caddell & Clare, 2010; Harré, 1991; Sabat & Collins, 1999; Sabat & Harré, 1992;) in which three aspects of the self can be derived through interactions of people with AD with other individuals or the interviewer. Self 1 is the experience of singularity or psychological continuity over time and can be determined by a person's use of personal pronouns such as "I", "me", "my", and "mine" and/or gestures such as pointing to one's self that index a person's unique and singular position in time and space. Self 2 refers to past and present physical and psychological attributes, beliefs, and judgment of these attributes. Self 3 consists of the persona that an individual displays socially, along with the attributes associated with that particular role, as a result of co-creation with one or more individuals (Harré, 1991; Sabat & Collins, 1999; Sabat & Harré, 1992).

Some studies report preservation of Self 1 in people with AD (Hedman, Hansebo, Ternestedt, Hellstrom, & Norberg, 2013; Sabat, 2002; Sabat & Collins, 1999; Sabat & Gladstone, 2010; Sabat & Harré, 1992; Tappen, Williams, Fishman, & Touhy, 1999), whereas others point to a potential loss, at least when measured by personal pronoun use (Fazio & Mitchell, 2009; Small, Geldart, Gutman, & Clarke Scott, 1998). However, those who report decreased or absence of personal pronoun use highlighted that people with AD were still able to defend their rights in conflicts and call staff by their names, which could be interpreted as demonstrations of the integrity of the self via non-verbal behaviors and manners of addressing people (Small et al., 1998). In addition, decreased usage of personal pronouns could mainly be a result of cognitive and linguistic production deficits rather than an inability to refer to one's self (Fazio & Mitchell, 2009). Reports on AD's effect on Self 2 have also been equivocal. Although the social constructionist framework states that Self 2 cannot be completely lost given that it consists of a person's actual physical and mental attributes (including the diagnosis of having AD) (Sabat, 2002; Sabat, Fath, Moghaddam, & Harré, 1999), it can still be affected by AD in a number of ways. Several studies reported the preservation of Self 2's self-reflection aspect as demonstrated by knowledge of past

attributes and acknowledgement of AD-associated deficits in language, movement, and memory and of challenges in taking care of several aspects of personal and family life (Hedman et al., 2013; Hedman, Hansebo, Ternestedt, Hellström, & Norberg, 2014; Sabat, 2005; Sabat & Collins, 1999; Sabat & Harré, 1992; Sabat et al., 1999). On the other hand, there were reports of a person with AD mixing past and present events, and several individuals who did not recognize or even markedly deny their memory deficits (Sevush & Leve, 1993; Skaalvik, Fjelltun, Normann, & Norberg, 2016). Finally, with regards to Self 3, someone with AD might prefer to be regarded according to his/her previous roles or professions rather than as someone suffering from AD (Sabat & Collins, 1999; Sabat & Gladstone, 2010; Sabat & Harré, 1992; Sabat et al., 1999). However, the expression of certain social selves might be limited due to healthy others limiting the social persona of a person with AD to that of a 'burdensome, dysfunctional patient' (Sabat, 2002, 2003) and to malignant positioning of healthy behaviors as dysfunctional and certainly due to the diagnosis (Sabat, 2005; Sabat & Gladstone, 2010; Sabat & Harré, 1992; Sabat et al., 1999; Sabat, Napolitano, & Fath, 2004).

Although the social constructionist framework has been the most employed model in studying the effects of AD on the self, other perspectives have also been used both in quantitative and qualitative studies. Among them is the interactionist perspective, indicating that the self is based on social constructs rooted in interactions with other people through conversations and non-verbal behavior (Caddell & Clare, 2010). Employing this perspective, Fontana and Smith (1989) noted that in certain people, the self is deteriorated to a point that only internalized social norms, basic emotional needs such as affection, and manifestations of selfishness remain in the person. Other qualitative studies employed the concept of embodied selfhood, which sees the self as reflected in bodily actions such as appearance, social etiquette, response to music, caring, politeness, and culture- and class-specific gestural communication and behavior (Kontos, 2004, 2005); and investigated the ability of participants to share personal narratives. These studies suggested that people with AD still have manifestations of selfhood through awareness of their surroundings, interaction with other people, and construction of an autobiographical memory-based narrative, albeit to varying degrees and with some individuals demonstrating chronological fragmentation or omission. Quantitative studies have utilized scales to evaluate the strength of identity in people with AD; role identities from the person's and family members' perspectives; self-recognition using mirrors, photographs, and videotapes; and knowledge of one's name, job, and personality traits, which are compared with ratings from family members. Overall, these studies show people with AD have a vaguer and weaker sense of identity; forget or place less significance in role identities, especially occupational roles; recognize themselves less likely in the mirror, videotapes, and recent photographs; and potentially, rate present attributes and personality traits less accurately (Caddell & Clare, 2010).

Overall, results from psychological and sociological studies on people with AD suggest that although selfhood is not completely lost in people with AD, several aspects of it can be affected by the disease at different stages. Given the number of overlaps in different frameworks used in qualitative and quantitative studies, other models can supplement and complete Harré's (1991) and Sabat's (2003) three aspects of the self to understand further the impact of AD on selfhood, acknowledging both verbal and non-verbal components and perspectives from the person with AD and his or her family and caregivers.

This extended version of the tripartite model of the self incorporates non-verbal forms of expression (Fontana & Smith, 1989), interactionist and embodied selfhood perspectives

(Kontos, 2004), and frameworks employed by quantitative studies (Caddell & Clare, 2010). Self 1 is now associated with personal pronoun use; subjective feelings, such as the feeling of being one's self; gestural actions that indicate singularity such as pointing to self, positioning of the body properly in space, and personal grooming; and self-recognition in front of a mirror (after acknowledgement of facing a mirror and in the absence of visual dysfunction). Self 2 encompasses actual past and present physical and mental attributes; awareness of these characteristics and their projection in day-to-day behavior outside social situations; and the general consistency of these descriptions over time and similarity with descriptions of family members and/or caregivers. We acknowledge that Self 2 cannot be completely lost in dementia or due to any other condition or intervention because the physical and mental changes they bring add to and become part of an individual's Self 2 (Sabat, 2005; Sabat et al., 1999). However, we aim to highlight other aspects of Self 2 that might be affected by AD or DBS and have relevance to caregivers, such as consistency of descriptions of physical and mental attributes and their portrayal in day-to-day life—aspects that can be measured through interviews with the person and his/her caretakers for a period of time and can be related to the severity of the disorder or parameters of the stimulation. Finally, Self 3 includes how a person acts socially or expresses values indicative of his/her past or present social role/(s) and positioning, and also how others interact with the person over time and whether or not that is consistent with the social role that he/she portrays. Although we acknowledge that this social role is co-created with the way others treat the person with AD (Sabat, 2003; Sabat et al., 1999) and that malignant social positioning can limit and negatively affect social relations (Kitwood, 1990), we do not discount the effects of neuropathological changes on cognition and behavior on how a person with AD acts in social situations (Cosentino et al., 2014; Rafii et al., 2014).

DBS for AD

Currently, two brain regions have been targeted to investigate if DBS leads to cognitive stabilization or improvement in people with AD. Some studies targeted the nucleus basalis of Meynert (NBM) (Kuhn et al., 2015; Turnbull, McGeer, Beattie, Calne, & Pate, 1985), the main cholinergic structure in the basal forebrain and is one of the structures severely atrophied in AD (see Liu, Chang, Pearce, & Gentleman, 2015 for an extensive review; Whitehouse, Price, Clark, Coyle, & DeLong, 1981; Whitehouse et al., 1982). The other region being targeted is the fornix, a white matter bundle connecting the hippocampus to the hypothalamus, nucleus accumbens, and septal nuclei (Oishi & Lyketsos, 2014). Phase I and Phase II trials have been/are being conducted in North America and France and have implanted 49 people with AD in total (Fontaine et al., 2013; Laxton et al., 2010; Lozano et al., 2016). These trials have been mainly driven by a serendipitous discovery on induced flashbacks and memory improvement in a person treated with hypothalamic/fornix DBS for obesity (Hamani et al., 2008).

A number of these DBS studies reported participants experiencing flashbacks of actual memories during in-surgery stimulation (Hamani et al., 2008; Laxton et al., 2010; Lozano et al., 2016) and also improvement or stabilization of scores in cognitive tests evaluating short-term memory, verbal fluency, object naming, and spatial and temporal awareness (Fontaine et al., 2013; Hamani et al., 2008; Kuhn et al., 2015; Laxton et al., 2010; Lozano et al., 2016). Interestingly, flashbacks have been observed in both people with and without AD. For instance, in the study that led to the Phase I and Phase II clinical

trials of fornix DBS for AD, Hamani et al. (2008) described that the person treated with DBS for obesity,

> Reported the sudden perception of being in a park with friends, a familiar scene to him. He felt he was younger, around 20 years old. He recognized his epoch-appropriate girlfriend among the people. He did not see himself in the scene, but instead was an observer. The scene was in color; people were wearing identifiable clothes and were talking, but he could not decipher what they were saying. As the stimulation intensity was increased from 3.0 to 5.0 volts, he reported that the details in the scene became more vivid. (Hamani et al., 2008)

The Phase I trial report also indicated that during in-surgery stimulation,

> Two of the 6 patients reported stimulation-induced experiential phenomena. Patient 2 reported having the sensation of being in her garden, tending to the plants on a sunny day with stimulation. In her case, this sensation outlasted the stimulation by several seconds. At certain contacts and settings, there was a pleasurable, warm sexual sensation that was clearly time-locked with the application of electrical stimulation. With stimulation, Patient 4 reported having the memory of being fishing on a boat on a wavy blue colored lake with his sons and catching a large green and white fish. On later questioning in both patients, these events were autobiographical, had actually occurred in the past, and were accurately reported according to the patient's spouse. (Laxton et al., 2010)

Although some participants experienced memory improvement or stimulation-induced flashbacks, a few of them also experienced adverse psychiatric events such as confusion, depression, and suicidal ideations. In the Phase II trial, participants <65 who were stimulated also experienced, on average, much faster cognitive decline than those who did not receive stimulation for one year (Lozano et al., 2016; Ponce et al., 2016).

These observations mirror the work of Wilder Penfield, who reported experiential phenomena induced by stimulation of certain regions in the temporal lobe in people undergoing surgery for epilepsy (Penfield & Perot, 1963). For instance, they reported that:

> As soon as the current was turned on, the patient exclaimed in great surprise, "Yes, Doctor, yes, Doctor! Now I hear people laughing—my friends in South Africa." He was asked if he could recognize who these people were, and he replied, "Yes, they are two cousins, Bessie and Ann Wheliaw." . . . This was a real experience and he was very surprised that he seemed to be with his friends back in South Africa which he had left about a month previously. (Case 38, 22-year-old man; Penfield & Perot, 1963)

However, novel issues arise with DBS in people with AD considering the vulnerable population being targeted due to their cognitive dysfunction, which may affect their capacity to consent; the progressive neuropathology and neurological damage caused by β-amyloid plaques and neurofibrillary tangles; the long-term nature of the stimulation; the region being stimulated; and the goal of the stimulation. Whereas Penfield and Perot (1963) performed cortical stimulation to mainly locate the epileptic focus, the studies on DBS for people with AD performed it on deeper structures (fornix or NBM) to determine if DBS could address the cognitive dysfunctions experienced as a result of AD and if successful in larger trials, have it as an approved therapy.

DBS and identity

DBS has been attributed by a number of people with Parkinson's disease (PD) to affect their own self-concept and to even lead to estrangement. For instance, some people experienced strangeness from the absence of motor symptoms; loss of vital force and aim in life; persistence of anticipatory thoughts on potential eventual motor problems; and an impression of a dehumanized and device-dependent body. Some people even perceived themselves post-surgery as an electric doll, a Robocop, or someone under remote control (Agid et al., 2006; Gilbert et al., 2017). Though these feelings could be a logical reaction to having a brain implant and also to the sudden disappearance of motor symptoms, which have affected people with PD for a long time, they could also be a result of the stimulation itself, the surgery performed, and/or accompanying adjustments in medication (Gilbert et al., 2017).

Aside from feelings of self-estrangement, there have been reports on the psychological and psychiatric effects of DBS for PD. For instance, amplification or decompensation of previously existing psychiatric disorders was observed, in addition to aggravation of personality traits related to lack of motivation, irritability, poor judgment, apathy, and vulnerability to pressure. There have been accounts of emotional hyperreactivity (Houeto et al., 2002), extroversion and a change in political affiliation (Mathews, Bok, & Rabins, 2009), development of a permanent manic state (Leentjens, Visser-Vandewalle, Temel, & Verhey, 2004), hypersexuality (Herzog et al., 2003), and stimulation-induced dissociative response (Goethals, Jacobs, Van der Linden, Caemaert, & Audenaert, 2008). As such, DBS for PD and other psychiatric conditions in which it is being tested could lead to unanticipated and negative psychological and psychiatric effects, which could not only threaten a person's identity but could also lead to diminution of agency.

DBS also has an impact on social relations of people with PD. General motor improvement from DBS did not guarantee proper social adjustment, or even resulted to impairment in certain individuals (Agid et al., 2006; Houeto et al., 2002; Schupbach et al., 2006). Some people reported lack of energy and wanting their spouses to just stay at home and care for them, whereas others exhibited sexually deviant and uncharacterized behaviors (Gilbert, 2017). On the other hand, dramatic motor improvements led to some individuals no longer wanting to become a dependent husband or wife and becoming more outgoing and independent, which resulted to some spouses having difficulties in giving up their roles as a caregiver and behaving as an equal partner rather than as a nurse (Schupbach & Agid, 2008). Other people developed novelty-seeking activities such as gambling and leisure tourism (Houeto et al., 2002). There have also been reports of people giving secondary importance to work, either as a result of realizing overinvestment in work pre-DBS to demonstrate competence in spite of PD or having less ability to concentrate in tasks (Agid et al., 2006), which could lead to decreased productivity and professional conflicts.

DBS for AD: Effects on the tripartite self

Self 1: Self-recognition, attribution, and referencing

Studies on DBS for AD are very preliminary, mainly focusing on cognitive and safety outcomes. None of them have performed in-depth interviews (Agid et al., 2006; Gilbert et al., 2017; Houeto et al., 2002). As such, there is no empirical information available to determine whether people with AD who received DBS also experience self-estrangement.

Almost all of the people enrolled are in an early to moderate stage of dementia, and as such, most of them potentially still have the capacity for self-recognition (Biringer & Anderson, 1992), although this was not measured in DBS for AD studies. Given that those at an earlier stage of AD could potentially better benefit from DBS (Laxton et al., 2010), the effect of DBS on diminished self-recognition will less likely be determined until this intervention has been approved for use in a wider population and in later stages of AD. Fornix DBS has also been shown to improve verbal memory (Hamani et al., 2008), which could potentially increase language use and thus, the use of first-person pronouns. However, simple increase in the use of first-person pronouns should not be treated as an increase in awareness of Self 1. Instead, the proportion and rate of first-person pronoun use (Fazio & Mitchell, 2009) should be employed to determine whether there is indeed an increase in self-ascription, in addition to the context in which they are used. Mere increase in the utterance of "I" should not easily be counted as a gain in the expression of Self 1 in the absence of its use to specify location, time, and/or responsibility (Harré, 1991). Moreover, the impact of improvement in ability to self-ascribe using first-person pronouns should be related to a potential increase in autonomy and independence and an improved ability to convey thoughts, emotions, preferences, and desires.

There is also no available information on whether DBS in people with AD leads to statements such as "I'm under remote control" (Agid et al., 2006), or "I wasn't me" (Gilbert et al., 2017). Given that some individuals with AD state "I have lost myself" when unable to progress with certain tasks (Maurer, Volk, & Gerbaldo, 1997), it remains to be determined whether DBS will aggravate this self-estrangement or if potential menory and cognitive improvements would allow individuals to "regain" themselves. The extent to which people with AD would be further estranged or would no longer feel estranged would largely depend though on initial perception of the disease, the extent of cognitive improvement, and on other unanticipated adverse psychological and psychiatric effects of the intervention. For instance, those who have dramatic memory improvements due to DBS could actually no longer feel estranged by their selves suffering from dementia, allowing them to return to their selves prior to dementia. The same could not be said for people who just experience minimal improvements or cognitive stabilization. These individuals, along with those who experience cognitive decline instead (Lozano et al., 2016), would potentially feel as or even more estranged by AD. In addition, those who develop adverse psychiatric events, such as delirium, depression (Lozano et al., 2016), or mania, could also have feelings of deteriorative estrangement, which can be manifested in lack of control over their emotions (Gilbert et al., 2017).

Self 2: Self-knowledge and identity continuity

In the revised tripartite model of the self, a person's physical and mental attributes are still important parts of Self 2 (Sabat & Collins, 1999), signifying that regardless of the extent of AD or cognitive dysfunction, a portion of Self 2 remains intact. Nonetheless, this does not mean that a person's Self 2 is immune to reduced richness (Seidl, Lueken, Thomann, Geider, & Schroder, 2011), fragmentation and petrification (Mograbi, Brown, & Morris, 2009), and negative perception by the person and others as a result of cognitive deficits, especially if they limit a person's daily activities of living and prevents him/her from properly navigating the world and interacting with other people (Maki, Amari, Yamaguchi, Nakaaki, & Yamaguchi, 2012).

Possible deficits in Self 2 due to AD could affect the narrative continuity of affected individuals, especially in the late stages where they fail to retrieve or encode recent memories (Seidl et al., 2011). Although philosophers such as Thomas Reid have argued that narrative continuity and ability to retrieve past memories are not essential components of selfhood (Copenhaver, 2014), other researchers in neuroethics have highlighted the importance of continuous personal narratives and psychological attributes in identity formation and maintenance (Klaming & Haselager, 2013; Schechtman, 2010). We subscribe that gaps or fragmentation in personal narratives and self-knowledge do not necessarily result to a loss of Self 2, considering its innateness to a person; however, we believe that discontinuities in narratives, a reduction in their richness, and diminished ability of self-assessment and self-knowledge could negatively affect Self 2. How much the loss of a particular memory threatens the Self 2 would be contingent on the emotional valence of the memory and their relationship to attributes that a person deems central to his or her identity. Although some people with AD who received DBS demonstrated positive changes in ADAS-Cog and MMSE scores (Kuhn et al., 2015; Laxton et al., 2010; Lozano et al., 2016), which might indicate increased intact recall leading to more correct answers in questions probing for memory, word recognition, language, orientation, and/or attention (Folstein, Folstein, & McHugh, 1975; Rosen, Mohs, & Davis, 1984), they do not necessarily mean that these people could already properly reflect on their present attributes or remember details of their past that would allow them to form a continuous narrative identity and adjust his/her personality and behavior. Improvements in MMSE and ADAS-Cog results due to DBS do not directly determine if a person with AD would suddenly be able to properly integrate ongoing experiences with his or her past experiences and could then properly make appropriate and voluntary behavior and personality adjustments. In addition, these tests would not be able to measure what "forgotten" past memories someone with AD will remember. If DBS only allows a person with AD to resume integrating and acknowledging present experiences but not recall memories "weakened" by AD, this could then create a memory gap, which could be seen as a disruption to a continuous narrative identity. Furthermore, there will be no way to retrieve experiences that have not been stored in the first place due to anterograde amnesia prior to treatment. It is also important to note that severe anosognosia in AD is actually associated with less severe depression (Starkstein, 2014), which might be due to decreasing awareness of cognitive deficits (Mograbi & Morris, 2013). As such, increased awareness of deficits in people with AD as a result of DBS-induced cognitive improvements might actually result in depression (Bianchetti & Trabucchi, 1999), especially if these improvements are just minimal or if the rate of cognitive worsening is just stabilized or slightly decreased. On the other hand, if they are dramatic enough such as in the case reported by Aquilina and Hughes (2006), wherein a person who had gone mute and had significant cognitive dysfunction was able to speak fluently again and even do crossword puzzles after taking a cholinesterase inhibitor, then this could lead to independence and a more positive evaluation of mental attributes and thus, an improved Self 2.

Potential DBS-induced adverse psychological effects (Agid et al., 2006; Gilbert et al., 2017; Houeto et al., 2002; Mathews et al., 2009), which could be seen as additional threats to the narrative continuity aspect of Self 2 (Klaming & Haselager, 2013; Schechtman, 2010), could also affect an already damaged Self 2 due to AD, albeit in varying ways. For instance, if a person who was initially depressed as a result of AD suddenly becomes manic as a result of DBS, then this might result in further disruptions in his or her narrative identity. However, this might depend on the person's personality prior to the onset of dementia.

Someone who is already energetic pre-AD would not really feel much discontinuity from DBS-induced elevated mood as opposed to someone who has been a shy and reserved person prior to AD. In fact, a pre-AD energetic person might even find these side effects as allowing him or her to express his/her true authentic self (Nyholm & O'Neill, 2016), which was "robbed off" by AD. Although someone who was previously shy even before AD might feel a sense of discontinuity, the extent of discontinuity would depend on how positive or negative does that individual sees being energetic as. If it is highly valued and seen as positive, the person might easily reconcile with this discontinuity, see it as empowering, and even feel elated, easily accommodating the newly acquired trait. It has to be emphasized though that a manic state post-DBS experienced by an individual might be authentic, acceptable, and preferable for him/her (Kraemer, 2013), but it does not necessarily suggest that his/her family and friends would also find that state desirable and authentic (Thomson & Segrave, 2017). These are hypothetical situations as no qualitative study investigating these phenomenon has been done in people with AD who underwent DBS; however, highlighting different scenarios is important in helping manage the expectations of trial participants on the potential consequences of participating in a DBS trial.

Fornix DBS has also evoked autobiographical memories in certain individuals (Hamani et al., 2008; Laxton et al., 2010; Lozano et al., 2016); however, it is unclear if these memories are those that someone can still fully recall and relive even in the absence of stimulation, or if they are forgotten memories, potentially due to AD, allowed to be accessed again and brought back to reminiscence by DBS. If these are memories that the person could still recall, replaying them might not really have profound consequences. However, if the evoked experiential phenomena are memories no longer accessible to the person with AD, DBS might actually positively impact Self 2 by allowing people to regain pieces of lost narratives and thus achieve better narrative continuity. This would also have a positive impact to caregivers and family members (Haahr, Kirkevold, Hall, & Østergaard, 2013). The content and emotional salience of the evoked memories should be greatly considered though. For instance, remembering the birth of a grandchild would have more significance rather than an evoked memory of just eating alone in an aged care facility. However, being reminded of a repressed traumatic memory such as an incident of abuse during childhood could potentially have negative effects on an individual. Although studies on the use of DBS in people with AD (Fontaine et al., 2013; Kuhn et al., 2015; Laxton et al., 2010; Lozano et al., 2016) have not mentioned any stimulation-induced traumatic or negative experiential phenomenon, one of Penfield's patients had a negative or threatening experiential hallucination during in-surgery stimulation (Patient 3). That patient suddenly saw robbers with guns coming at him; however, this was not an actual past experience but rather a fantasy drawn from reading a comic book (Penfield & Perot, 1963). The difference in the region stimulated and the parameters might have an influence; however, the possibility of a negative and distressing experiential phenomenon should not be disregarded.

Self 3: Relational identity and social positioning

The actual impact of DBS for AD on participants' social adjustment remains to be determined since none of the performed studies on DBS for AD have utilized a Social Adjustment Scale measure similar to what studies on PD have employed (Agid et al., 2006; Houeto et al., 2002; Paykel, Weissman, Prusoff, & Tonks, 1971). However, it is possible to anticipate the potential impact of DBS in the Self 3 of people with AD based on

differences in people with AD and PD. First, most DBS for AD trial participants are in the mild to moderate stages of dementia, and as such, still retain functional capacity and ability to engage in certain social roles as opposed to those with PD who might be severely disabled by their motor symptoms. Certain functional capacities and an ability to engage in certain social roles might even be retained in severe disease stages in AD (Kontos, 2004; Sabat et al., 1999), albeit to varying degrees depending on the extent of brain pathology and the existence of malignant positioning by others (Kitwood, 1990; Sabat & Gladstone, 2010; Sabat et al., 1999). Since DBS has not been tested in people with severe AD, it is not yet known how dramatic and enduring will the cognitive improvements be. Regardless of disease stage, it is vital to highlight that an important aspect of Self 3 is the way others treat the person with AD, which fundamentally creates the social identity that he/she projects, underscoring the influence of caregiver expectations post-DBS on the ability of a person with AD to express certain social selves. Second, the average age of DBS for AD recipients is also much older than those who usually receive DBS for PD (Agid et al., 2006; Lozano et al., 2016). Majority of people with AD who underwent DBS surgery are greater than 65, and as such, might have already retired from work and no longer have professional commitments (Organisation for Economic Co-operation and Development, 2016). For those who no longer have active professional commitments and have already retired, potential adverse effects in professional relations due to people giving secondary importance to work after DBS in people with PD (Agid et al., 2006) might not be encountered.

Considering the aforementioned differences, the effects of DBS on the familial and professional Self 3 of someone in early-stage AD might not be as dramatic as in those who are in PD, especially for people with mild to moderate AD. Cognitive improvements from DBS, especially if they are not dramatic, in people with mild AD might not result to regaining of functionality that is as pronounced as in PD. If DBS just reduces the rate of cognitive decline, people with AD might not even feel the effects of the treatment and might even continue to experience cognitive decline, albeit at a slower rate. However, the extra time that DBS affords these individuals could actually allow them to be more confident in living up to their present roles and function optimally for a longer period of time. For instance, a grandmother would still be able to read story books for her grandchildren and answer questions from them, or an academic would be able to teach and write papers for a longer period of time. For people in late stages of AD, it can only be hypothesized that the effect of DBS on someone's social confidence would largely be contingent on how dramatic cognitive improvements it could cause are. If they are large enough for someone to regain communication, executive, and navigation skills, then it would also be possible for these individuals to pursue novel things and resume past activities, similar to the case of Mrs. G who was mute but started to talk again and verbally interact with other people as a result of dramatic cognitive improvements from a cholinesterase inhibitor (Aquilina & Hughes, 2006). These might result to a similar situation for those with PD wherein a gain of independence has affected someone's dependence on his/her spouse or children, consequently affecting marital and familial relations.

Although some social issues relate to people feeling overly empowered post-DBS, other individuals feel the inability to properly resume normal activities due to the negative consequences of PD on the person's life and the burden/pressure attached to being "normal" once again (Agid et al., 2006; Gilbert, 2012). The initial damage done by AD on an individual's life, especially on his social relations, could also lead to problems in social adjustment. Cognitive deficits in people with AD could make them feel unable to socially

demonstrate attributes they had in their careers (Sabat, 2002) and when coupled by stigmatizing and discriminating attitudes of people towards them (Baylis, 2013; Werner, 2008), could inevitably result in them less likely to engage in social situations. These feelings might persist even after DBS, especially when the stimulation does not really result to improvements but rather just stabilizes cognition or decreases the rate of cognitive decline. In addition, even if there are significant improvements, some people with AD might still find it difficult to discard the pathology from their self-image (Gilbert, 2012) and still feel insecure when in social situations. Expectations by family members would also play a great role in the social selves that people with AD portray. If after DBS, other people would treat the DBS recipient as someone who is more "capable", though AD might not have necessarily incapacitated him or her and these perceptions of incapacity are just due to malignant positioning, the person would be given more opportunities to express his/her Self 3 and better enrich his/her social life. The possibility of too high expectations is also possible and could lead to social adjustment issues, especially when spouses of people with AD would potentially reject them following DBS, thinking that DBS would allow the person with AD to return to a life prior to disease onset (Agid et al., 2006). Although spouses might expect restoration of independence in people with AD, cognitive improvements might not be dramatic enough to regain normal function. This could lead to undue pressures to the person with AD and could even make them feel a diminished Self 3 due to their inability to fulfill the expectations of their wives, children, and/or caregivers. Furthermore, this might result to reduced care and monitoring due to a misled sense of belief that DBS in people with AD is an actual therapy that leads to improvements in cognition rather than an experimental intervention.

Ethical implications for consent and care

Several international recommendations and standards such as The Helsinki Declaration, the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subject, the Oviedo Convention on Human Rights and Biomedicine, and the 2001/20/European Commission Clinical Trials Directive emphasize the need for protection of vulnerable subjects, especially those with limited capacities to consent (Duguet & Boyer-Beviere, 2011). Significantly greater protections should be provided for vulnerable research participants in studies where the possible harm is greater than those encountered in their everyday life, in addition to ensuring that the study has potential direct benefit to the participants (Beattie, 2007). Considering the cognitive deficits in people with AD that could limit their ability to provide fully informed consent (Cahill & Wichman, 2000) and the risks associated with DBS (Patel et al., 2015), the informed consent process for DBS in people with AD has to be adapted to ensure maximal understanding of involved parties while acknowledging potential limitations in the ability of people with AD to fully comprehend the trial procedure. Furthermore, the potential iatrogenic harms on the use of DBS in people with AD raise serious ethical concerns, beyond bodily harms associated with safety concerns and potential impacts on a recipient's psychological life and existence. This highlights the relevance of the tripartite model of selfhood in ensuring that the physical, mental, and social well-being of participants are well-protected and that their selfhood is acknowledged and honored before, during, and even after the trial, in line with the bioethical principles of beneficence, non-maleficence, and respect for autonomy (Beauchamp & Childress, 2013).

Given that Self 1 can be intact in people with AD, as demonstrated by the use of first-person indexicals (Hedman et al., 2013; Sabat, 2002; Sabat & Collins, 1999; Sabat & Gladstone, 2010; Sabat & Harré, 1992; Tappen et al., 1999) and gestures that refer to one's self (Kontos, 2004), the opinions of people with AD regarding trial participation should always be considered. Even if they have been assessed to have limited capacity to consent using standardized measures of capacity assessment (Grisso, Appelbaum, Mulvey, & Fletcher, 1995; Marson, Ingram, Cody, & Harréll, 1995), their assent should still be obtained and any consistent manifestations of dissent should be honored (Siegel et al., 2017). There should be no way that only a legally assigned representative (LAR) or a surrogate's decision be adequate in trial participation; however, their consent also has to be obtained for a person with AD to be enrolled in a DBS trial. Double informed consent (Beck & Shue, 2003) would ensure that there will be someone to eventually make fully informed decisions once the participant's capacity to make well-informed judgments has been compromised, especially with DBS trials that can run for up to four years (Lozano et al., 2016). It is however important that the person providing the second consent also has adequate decision-making capacity. Finally, we recommend that people with AD who do not have adequate capacity to consent or do not have another person to provide additional consent should not be included in clinical trials on DBS for AD (Viaña, Bittlinger, et al., 2017). This would ensure that should someone with AD who is undergoing DBS reaches a stage where his/her abilities to consistently and properly use first-person indexicals, indicative of acknowledgement of his/her social position as an autonomous decision-maker, have been diminished (Fazio & Mitchell, 2009; Small et al., 1998), a close family member, caretaker, or LAR is available to appropriately indicate the person's preferences (based on what they know of the person's past autonomous choices) and act as an extension of the person's Self 1.

Although Self 2 may not be lost due to AD, it can be negatively affected should DBS induce adverse psychiatric events that might disrupt a person's psychological continuity—in a deteriorative and distortive way (Gilbert et al., 2017). Furthermore, cognitive deficits due to AD might further impair the capacity of a person with AD to make fully informed and carefully evaluated decisions in later stages of the trial. Both possibilities highlight the need for the issuance of advance directives upon enrollment in the trial and also the assignment by the patient of an LAR or a surrogate-decision maker, who knows the participant's preferences and could make decisions that would uphold them. Given that the intervention itself might result to unwanted changes in the Self 2, these should be relayed to the participant during the informed consent procedure, in addition to the outcomes that the trial aims to evaluate. However, most informed consent procedures under-emphasize potential adverse effects of the intervention on social function and selfhood and just present immediate and long-term medical risks. Informed consent procedures could be augmented in a way that presents both known medical risks, risks of unknown prevalence, unknown risks (Lipsman, Giacobbe, Bernstein, & Lozano, 2012; Maslen et al., 2018), and hypothetical risks. These hypothetical risks, such as the recollection of traumatic childhood memories during in-surgery stimulation (Penfield & Perot, 1963) or deteriorative feelings of powerlessness that have been correlated with self-harms (Gilbert, 2013; Gilbert et al., 2017), can be determined from interventions that have a great degree of similarity to the one being evaluated (DBS for PD, cortical stimulation). It is also advised that the informed consent procedure be performed by an external party to minimize the influence of the study doctors on the decision of the person with AD and his or her family to participate in the trial, in addition to

involving people such as social workers to help evaluate and relay potential impacts of DBS to the research participant and his/her family members (Glannon, 2010). Finally, considering that certain adverse events, such as recollection of traumatic memories or threatening situations (Penfield & Perot, 1963), emergence of psychiatric symptoms and feelings of loss of control or powerlessness (Gilbert, 2013, 2015; Gilbert & Viaña, 2018, in press; Gilbert et al., 2017), and accelerated cognitive decline (Lozano et al., 2016), could arise and could negatively affect a person's Self 2, proper counseling strategies, frequent monitoring, and adequate support and care should be provided all throughout the trail and for a certain period after the trial.

Finally, trials should ensure that participants are not just delegated as mere participants or patients but rather be allowed to express themselves as research collaborators, facilitating the respect and enrichment of their Self 3 (Sabat, 2003). Participants should be involved in discussions regarding trial participation, consulted regarding potential changes in the protocol, and informed of the results once the trial is finished. Furthermore, qualitative and quantitative measures of social function should be incorporated as outcomes (Agid et al., 2006; Houeto et al., 2002; Kitwood, 1990; Paykel et al., 1971; Sabat & Gladstone, 2010), given their importance in a participant's everyday functioning. Caregivers should also be briefed and provided adequate information regarding certain psychosocial effects as a result of DBS to allow proper adjustment, prevent malignant psychology, and also minimize therapeutic misconceptions (Siegel et al., 2017) that might lead to hyper-inflated expectations. These information should not only be brought up during the informed consent procedure, but they should also be consistently relayed all throughout the trial. In the event that stimulation results to drastic effects that trample with the person's dignity and cause significant distress and confusion, adequate care and support should be provided at all times to acknowledge the person's pre-existing social role and allow him/her to still project and create preferred Selves 3. Honoring the person's intact capacities and personhood (Kitwood, 1990) could help promote a degree of independence and help maintain competence to make autonomous decisions that are in his/her best interests.

Conclusions

Overall, we used an extended tripartite model of the self grounded on Harré's (1991) and Sabat's (2002) social constructionist framework to hypothesize the potential impacts of DBS on the selfhood of people with AD using information from clinical trials and case reports. We acknowledge that the three "selves" we proposed are not mutually exclusive and actually have several overlaps. For instance, an intact Self 1 is needed in order to be able to reflect on one's personal attributes (Self 2) and exhibit them in appropriate social situations (Self 3). In addition, we also do not intend to speculate on whether the overall selfhood, Self 1, Self 2, or Self 3 is lost in people with AD who receive DBS as we see each aspect of the self as further divided into distinct components that actually exist as a continuum rather than as a binary entity, with the effects of DBS and AD highly contingent on the disease stage, extent of improvement, potential treatment-associated adverse effects, and social positioning by others.

By highlighting three aspects of the self and multiple dimensions of each aspect, we hope to have provided a critical overview and examination of the possible impacts of both AD and DBS on individuals and have emphasized the need for a multi-perspective and multidisciplinary approach towards understanding the concept of selfhood. Furthermore, the

ethical recommendations we have provided would be applicable not only to existing and future trials employing DBS in people with AD, but also to other forms of invasive and non-invasive interventions. Examining ethical issues for an intervention through its potential effects on Self 1, 2, and 3 of a person with AD acknowledges that AD is not only a disease of the brain and cognition, but is a disorder that has a rich social dimension that needs to be taken into account when designing and conducting a clinical trial.

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SECTION IV.

Discussion and Conclusions

Chapter Seven. Extending the Neuroethical Discussion and Moving Forward

I. A Multi-Level and Interdisciplinary Approach Towards Elucidating Ethical Issues

Interdisciplinarity is one of the key features and driving forces of neuroscience, from the formalization of the first neuroscience institutes and establishment of dedicated organizations such as the Society for Neuroscience (SfN) and the International Brain Research Organization (IBRO) (Sabbatini & Cardoso 2002) to the present endeavours in broadening and deepening the understanding of brain processes and the way they result to consciousness, cognition, and behaviour. By bringing together the expertise of people in biology, chemistry, physics, mathematics, computer science, engineering, and psychology, knowledge on how the brain works has vastly improved. Not only has there been interdisciplinarity in the disciplines that converged to develop the tools and contribute to the baseline knowledge for neuroscientific inquiry to flourish, but also in the levels of organization in which mental processes are being investigated. As highlighted by Sabbatini and Cardoso (2002), neuroscience has leveraged research focus from just a single organisational level to a more integrated and multi-directional approach, acknowledging molecular, cellular, network, psychological, and socio-environmental contributors to cognition and action.

Given the interdisciplinary nature of neuroscience, it is just befitting for a field that investigates and explores the ethical dimensions of this discipline to acknowledge the benefits of looking at different levels of biopsychosocial organization and through different disciplinary lenses. Furthermore, from a pragmatic standpoint (Fins, Bacchetta & Miller 1997; Racine 2008b), understanding the ethical and societal implications of neuroscientific development

necessitates the use of empirical knowledge and methods from both the natural and social sciences, taking into account scientific facts and social norms. As such, this project investigates neuroethical issues on clinical trials of deep brain stimulation for Alzheimer's disease from the perspectives of medicine, psychology, sociology, and philosophy. This project incorporates knowledge from neuroscientific research on the genetic, molecular, cellular, and structural underpinnings of AD, along with psychological and sociological investigations on how it affects the cognition and shapes the lived experience of those diagnosed with it, to determine and dissect ethical issues associated with the potential use of DBS as another mode of therapy for people with AD.

By grounding the claims made throughout this thesis on actual results of the case studies and trials on DBS for people with AD (Turnbull et al. 1985; Laxton et al. 2010; Fontaine et al. 2013; Kuhn et al. 2015; Lozano et al. 2016) and on studies reporting its effects for other conditions such as that of Gilbert et al. (2017) and Gilbert and Viaña (2018) in Chapter 3, this dissertation aims to provide recommendations that would be relevant and relatable to people with AD, their family and caregivers, their attending medical team, and the doctors and scientists conducting the clinical trials. Pragmatically-oriented (Fins, Bacchetta & Miller 1997; Racine 2008b) conceptual work on this topic could serve as the basis of future actual empirical work involving deliberation and engagement with various key stakeholders, allowing better understanding of the perspectives of people with AD on participating in a risky and invasive clinical trial and the intentions and motivations of researchers in extending the application of DBS to AD. This study also acknowledges the richness that philosophical inquiry brings to the understanding of the effects of DBS for AD on selfhood, as illustrated by the descriptive enumeration of several philosophical viewpoints in Chapter 3 and their use in the publications

incorporated in the same chapter and in Chapter 6. Viewing empirical data through the philosophical propositions made on how DBS could affect identity and selfhood would further enrich the ethical issues raised and recommendations made, as long as the claims are not overhyped and are still well grounded on empirical realities, a point emphasized in the paper of Gilbert, Viaña and Ineichen (2018) in Chapter 3.

Keeping in mind the different levels of biological organization, the reviews on clinical trials of DBS for AD in Chapters 4 (Viaña et al. 2017) and 5 (Viaña, Bittlinger & Gilbert 2017) present whether these trials performed genetic tests or incorporated biomarkers in recruiting participants; what cognitive, neurologic, and psychiatric characteristics were used to determine the people with AD eligible to participate in the trials; the stimulation parameters used; and the medical, cognitive, neurologic, psychiatric, and functional outcomes utilised to assess the safety and efficacy of the procedure. Constructing tables in these publications allowed easier comparison of protocols among different trials and identification of differences, which could hint to salient ethical issues that need to be raised.

By looking at Table 3 in Chapter 4 (Viaña et al. 2017), it is evident that other fornix DBS for AD trials (Laxton et al. 2010; Fontaine et al. 2013) did not have suicidal tendencies or history of suicide as an exclusion criterion, although it is a potential risk associated with DBS (Appleby et al. 2007). It is also apparent in Table 1 in Chapter 4 (Viaña, Bittlinger & Gilbert 2017) that only few studies (Fontaine et al. 2013; Kuhn et al. 2015) used biomarkers such as CSF tau and $A\beta_{42}$ to ascertain that their participants really have Alzheimer's pathology. Considering that the trials propose the use of DBS for people with Alzheimer's disease, additional tests, especially if they are already available and have even been used by other DBS

for AD studies, to ascertain the diagnosis should be utilised to increase the scientific validity of the findings and to exclude people who might have dementia that is not due to Alzheimer's pathology from participating in a risky and highly invasive trial. Also, since a lot of studies included people who are <65, these individuals could have frontotemporal dementia (FTD) due to the early onset of dementia symptoms, which could affect the study's internal validity and also the outcome for these participants given the variability in affected brain networks between people with AD and FTD (Hafkemeijer et al. 2016).

In addition to showing the different levels of biological organisation used for recruitment and assessment in DBS for AD trials in humans, scrutinizing the effects of fornix DBS stimulation in different animal models on molecular, cellular, structural, electrophysiological, and behavioural parameters also help identify significant translational issues and possible risks of harm from DBS, which can then be used to propose refinements for in-human trial protocols (Viaña et al. 2017).

In Table 2 in Chapter 4 (Viaña et al. 2017), it can be seen that only very few studies utilised animal models in which AD-associated cognitive deficits (Hescham et al. 2017) or pathophysiological processes (Zhang et al. 2015) were deliberately induced. This could affect the translatability of findings on the effects of fornix DBS not just on memory, but potentially, also on molecular, cellular, and network properties given the absence of AD-associated deficits in the animals used in most of the studies. Another important translational issue, which also has serious ethical repercussions, was derived from results of the study of Talakoub et al. (2016), which suggested that improperly timed stimulation could actually disrupt brain activity critical in memory consolidation or retrieval. Although this study did not

perform any behavioural tests to determine whether such disruption really affected the memory of the macaque monkey being tested, it highlights the need for close monitoring of participants given the possibility of memory impairment as a result of inappropriate stimulation parameters or timing. It would be ironic and harmful to participants with AD that an intervention being tested to address memory deficits would in itself be detrimental to proper memory function.

In Chapters 4 and 5, the ethical issues raised were divided according to when in the development of the technology or in what stage of the trial they will arise. The purpose of this is to encourage critical reflection of scientists and doctors facilitating these pre-clinical studies and/or in-human trials on what considerations should they make in designing, executing, and concluding an animal study or a clinical trial in humans. This mode of division is also in line with framework for determining ethical issues in clinical trials forwarded by Emmanuel, Wendler, and Grady (2000) and by Li et al. (2016). Publishing the papers making up Chapters 4 (Viaña et al. 2017) and 5 (Viaña, Bittlinger & Gilbert 2017) in medical and neuroscientific journals would hopefully increase readership of these articles by medical and scientific professionals conducting DBS for AD studies and facilitate the integration of the recommendations provided in studies that they are or will be conducting.

Starting with translational challenges, the discussion on this issue in Chapter 4 highlights the need for a close collaboration between scientists testing the technologies in animal models and to people doing the clinical trials to maximise the translatability of findings, especially with regards to the stimulation parameters and timing during the disease course and the relevance of observed outcomes in animals to physiological and functional measures

in humans (Viaña et al. 2017). The "Participant selection criteria" section in Chapter 4 (Viaña et al. 2017) and the "Considerations for patient selection" section in Chapter 5 (Viaña, Bittlinger & Gilbert 2017) both discuss ways in which the selection criteria can be improved to ensure that participants are not subjected to undue and avoidable harms and also potentially benefit from the procedure, in line with the ethical principles of beneficence and non-maleficence (Beauchamp & Childress 2013) and with pragmatism's (Fins, Bacchetta & Miller 1997; Fins 2008b) goal of providing practical goals and realizable plans of action. This is evident in the suggestions on excluding people with suicidal tendencies and/or depression, including only people with mild AD if they are <65 and have EOAD-associated genetic mutations, and incorporating biomarkers for AD pathology in the selection criteria. The "Trial design" section in Chapter 4 (Viaña et al. 2017) and the "Disease progression and study design" section in Chapter 5 (Viaña, Bittlinger & Gilbert 2017) evaluate the study designs of different clinical trials to see whether participants assigned to a certain study group could be disadvantaged, especially if they do not get access to the intervention for a particular time period and if by the time they would, the potential "therapeutic window" has already been missed considering the degenerative nature of Alzheimer's disease. The "Outcome measures" section in Chapter 4 (Viaña et al. 2017) and the "Potential trial outcomes" section in Chapter 5 (Viaña, Bittlinger & Gilbert 2017) examine the measures used to evaluate the safety and efficacy of the intervention and also the time points in which these evaluations were made. These sections also highlight the need for determining the relevance of these measures to the quality of life and lived experience of people with AD and how expectations regarding potential benefits from trial participation are managed. Finally, Chapter 4 (Viaña et al. 2017) touches on institutional (Fins, Bacchetta & Miller 1997), economic and societal issues, particularly on challenges to access of DBS for AD should it be eventually approved and also

on the potential misuse of safety and efficacy data from clinical trials to offer DBS in people with AD as an off-label therapeutic option outside the context of a clinical trial.

As evident in the discussion in the preceding paragraph, the format in which the ethical issues were raised in Chapters 4 and 5 are pretty similar. Nonetheless, the paper in Chapter 5 (Viaña, Bittlinger & Gilbert 2017) brings additional scientific information and further ethical reflection by highlighting that although general ethical considerations can be made for a particular neurotechnology such as DBS and on its application for a novel condition such as AD, ethical analysis can even be extended and made more specific to account for issues that would arise from variable results of an intervention between sub-populations (Lozano et al. 2016), in line with pragmatism's (Fins, Bacchetta & Miller 1997; Racine 2008b) emphasis on the role context in ethical deliberation.

The differing results between participants who are <65 and participants who are ≥65 (Lozano et al. 2016) suggest that factors such as age or the presence of autosomal dominant AD-associated mutations, which could result to earlier onset of dementia (Cacace, Sleegers & Van Broeckhoven 2016), might play a role and should be accounted for in determining the populations to recruit and the way that the trial will be designed and executed. Incorporating genetic information into the trial also necessitates additional ethical considerations, which are elaborated in the "Genetic vulnerability and informed consent" section in Chapter 4 (Viaña, Bittlinger & Gilbert 2017). By drawing from literature in genethics and genetic counselling, this section discusses issues relevant to disclosure of genetic results and the need for pre- and post-test counselling, and potential problems that could arise when the participant and his/her family have differing opinions on the conduct of a genetic test for AD-

associated mutations. Although concerns on the risks of genetic information to an individual with AD could be lessened if there is already a clear diagnosis of AD, some other risks to that person and to his or her family members remain. For instance, information on having autosomal-dominant mutations linked to early-onset AD could lead to prognostic pessimism (Kong, Dunn & Parker 2017) on some individuals regarding their rate of decline and possible eventual appearance of behavioural (Cacace, Sleegers & Van Broeckhoven 2016) and motor symptoms (Wu et al. 2012) associated with autosomal dominant AD, especially in the absence of proper post-test genetic counselling (Viaña, Bueno & Gilbert 2017). Genetic information could also have repercussions on family members, primarily on children and immediate relatives. A positive genetic test result for possession of autosomal dominant AD associated alleles means that children and siblings could also have the mutation, which would have implications on insurance (Roberts, Christensen & Green 2011), reproductive (Goldman 2012), and geriatric care planning, in addition to decisions on participating in a clinical trial for those with autosomal dominant AD (Van Cauwenberghe, Van Broeckhoven & Sleegers 2015) and getting a genetic test themselves. Chapter 5 also includes a section on "Interpretation and communication of study results", which emphasizes the need for transparency in disclosing challenges encountered during the trial, adverse events experienced by the participants and the way they were managed, and results for all the statistical tests performed. This section also proposes additional analyses that can be performed, such as accounting for genetic data or cognitive scores at the start of the trial, to ascertain if age has a direct effect on a participant's response to the intervention and also to better refine the recruitment criteria in future trials, ensuring that only those with the greatest prospect of benefit and least risk of harm are recruited.

Although a few of the recommendations on patient selection, trial design, and measured outcomes presented in Chapter 4 (Viaña et al. 2017) were re-iterated and emphasized further in Chapter 5 (Viaña, Bittlinger & Gilbert 2017), new ones were also proposed to account for differences between EOAD and late-onset AD. These include recruitment of people <65 who only have a milder form of cognitive dysfunction, especially when they have autosomal dominant genetic mutations predisposing them to EOAD; shortening the time when stimulation would be withheld from the <65 group; having a more frequent outcome assessment; and including additional measures that determine the effects of DBS on dysfunctions such as apraxia, aphasia, and dysexecutive syndrome, which are more prevalent in people with early-onset familial AD (Wu et al. 2012).

Overall, the paper of Viaña, Bittlinger and Gilbert (2017) demonstrates the value of looking more closely at peculiarities in clinical trial results and understanding what ethical issues and concerns could emerge from them, particularly from the perspective of those that could be harmed to a greater degree as a result of assignment to a certain trial arm. This paper also highlights how bringing together discussions from different ethical disciplines such as neuroethics and genethics could result to a better understanding of important ethical issues and to the proposal of practical (Fins, Bacchetta & Miller 1997; Racine 2008b) recommendations that account for multiple dimensions of the disorder and its effects on afflicted individuals and their family.

As mentioned at the start of this section, neuroscientific knowledge has benefitted greatly from interdisciplinarity, both in the levels of organisation investigated and the

disciplinary tools employed (Sabbatini & Cardoso 2002). The same applies for knowledge on specific disorders such as AD and the effect of an intervention such as DBS.

Whereas the papers in Chapters 4 (Viaña et al. 2017) and 5 (Viaña, Bittlinger & Gilbert 2017) focus more on the medical and scientific aspects of DBS and AD, Chapter 6 (Viaña & Gilbert 2018) widens the investigative lens and incorporates reflections from psychology, sociology, and philosophy to anticipate the effects of DBS for AD on selfhood and identity and uses these as springboards in determining salient ethical concerns. Although the model of selfhood used is primarily based on the one proposed in the publications of Sabat and Harré (1992) and Sabat and Collins (1999), Viaña and Gilbert (2018) acknowledge that the original social constructionist-grounded tripartite model of selfhood only focuses on verbal components of Selves 1, 2, and 3. As such, the original tripartite model was extended, incorporating other frameworks used in the investigation on the effects of AD on selfhood and identity that were mentioned in Chapter 2, to provide a more comprehensive theoretical framework that will be employed to hypothesize the effects of DBS on the selfhood and identity of people with AD.

By combining results from DBS for AD trials, with a focus on the experiential phenomena experienced by some participants during in-surgery stimulation, with qualitative studies or philosophical reflections on the effects of AD or DBS on selfhood and identity, which were reviewed in Chapters 2 and 3, we attempt to provide reflections that are philosophically encompassing yet empirically grounded, in line with the pragmatic framing and practical inclination (Fins, Bacchetta & Miler 1997; Racine 2008b) of this dissertation. This way, the hypothesised effects of DBS for AD on Self 1 or self reference and attribution; Self 2 or one's

characteristics and life story, and knowledge of them; and Self 3 or social and relational projection of the self would still resonate with and be relatable to people with AD and their caregivers (Viaña and Gilbert 2018).

Using the revised tripartite model of selfhood as a lens to examine ethical concerns arising from DBS for AD studies reinforces some of the recommendations made in Chapters 4 (Viaña et al. 2017) and 5 (Viaña, Bittlinger & Gilbert 2017), especially with regards to acknowledging the remaining capacity of a participant in the informed consent process, creating an advance directive, and assigning a legal representative and/or a co-decision maker. In addition, fleshing out the ethical issues based on DBS for AD's possible effects on the tripartite self facilitate the suggestions of additional recommendations on the presented information during the informed consent procedure, preparation for adverse events such as recollection of traumatic memories, treatment of the participant as a research partner in the trial, incorporation of social adjustment measures in the assessment of DBS-associated sequelae, and proper communication with the participant and his/her caregivers on the possible extent of benefit from the treatment to prevent misconceptions and unrealistic expectations (Viaña & Gilbert 2018).

In conclusion, the three papers presented in Chapters 4 (Viaña et al. 2017), 5 (Viaña, Bittlinger & Gilbert 2017), and 6 (Viaña & Gilbert 2018) provide a multi-level interdisciplinary analysis of clinical trials on DBS for AD and the ethical issues that arise from them. Hopefully, such approach has illustrated the richness, diversity, and complexity of issues associated with DBS for AD; and has provided a discourse that people with AD, their family and caregivers, doctors, neuroscientists, social scientists, and philosophers could understand, relate to, and

participate in. It is important to acknowledge that while majority of the statements and claims in these publications are empirically grounded and based on observations from other DBS studies or research involving people with AD, this project remains a conceptual and theoretical one. As such, some of the claims such as recollection of traumatic memories or increased risk of suicide might not be observed in people with AD who receive DBS. Nonetheless, acknowledging the possibility of these events would lead to measures, such as exclusion of people with depression, that would prevent them from occurring in the first place and properly address them should they arise. In order to adopt a full pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b), recommendations in the three main publications should be tested and deliberated upon in future empirical bioethical studies involving people with AD who have received or will receive DBS, and on future conceptual and empirical neuroethical research on new findings from the clinical trials examined (Leoutsakos et al. 2018), or on DBS of other brain regions (Scharre et al. 2018) or DBS with a closed-loop set-up (Senova, Chaillet & Lozano 2018) in people with AD.

II. DBS and Beyond: Extending the Ethics to Other Invasive Neurotechnologies

The pragmatic (Fins, Bacchetta & Miller 1997; Racine 2008b) analytical framework used (examination of issues during different translational and clinical trial stages; identification of novel considerations as a result of variable results in different sub-populations; and using a philosophically, psychologically, and sociologically-grounded tripartite model of selfhood) and ethical recommendations made in this dissertation can be applied not only to future DBS for AD studies but also to other invasive neurotechnologies that are being tested for people with Alzheimer's disease.

In addition to DBS, other invasive neurotechnologies such as stem cell implantation and gene therapy have been or are being tested in people with AD. The commentary of Viaña, Carter, and Gilbert (2018), which can be found in pages 193 to 198, presents graphs demonstrating that in recent years, there has been an increase in the number of studies and in the number of people with dementia recruited for trials involving DBS, stem cell therapy, or gene therapy. Considering the rapid pace of biotechnological innovation, these numbers are expected to continuously increase.

Gene therapy trials involve delivery of deoxyribonucleic acid (DNA) into the central nervous system, either *ex vivo* by implanting genetically modified cells containing the therapeutic gene or *in vivo* by directly introducing a therapeutic gene into the desired region using viral vectors (Choong, Baba & Mochizuki 2016). An example of a gene therapy study being conducted in people with AD is that of Rafii et al. (2014) wherein adeno-associated virus (AAV) particles containing the nerve growth factor (NGF) gene are delivered stereotactically to the nucleus basalis of Meynert (NBM), a brain region with densely packed cholinergic neurons, which provides majority of the cholinergic input to the entire neocortex (Rafii et al. 2014).

In the trial of Rafii et al. (2014), ten people with mild to moderate AD (MMSE of 16 to 28) received bilateral AAV2-NGF injections into the NBM. The participants were divided into three groups, with each group receiving a different dose of AAV2-NGF (1.2×10^{10} viral genomes (vg), 5.8×10^{10} vg, or 1.2×10^{11} vg). They were assessed at several time points, with the earliest one a day after the surgery and the latest one, two years post-surgery.

In terms of safety, there were no unusual surgical complications except for a postsurgical hygroma, which was successfully drained. There were very few adverse events, all of which were deemed by the investigators to be not or unlikely related to the intervention. Only one participant died during the 24-month observation period, with the cause being failure to thrive (Rafii et al. 2014), which is a syndrome of weight loss, decreased appetite and poor nutrition, decline in physical and cognitive function, and inactivity (Sarkisian & Lachs 1996). It was not specified though if this has been the result of the Alzheimer's pathology or if the intervention had any role in it.

For secondary clinical outcomes, Rafii et al. (2014) reported the absence of any evidence suggesting a rate of clinical deterioration greater than that of people with mild to moderate AD who were enrolled in previous studies. They also mentioned that participants who received the highest dose of AAV2-NGF deteriorated the least based on Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) and Mini-Mental State Examination (MMSE) scores. Furthermore, there was only mild to sub-moderate deterioration in the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCSCGIC) test for all three groups, and there were also no significant differences noted on other neuropsychological measures.

Post-mortem pathological assessments were performed on the brains of five participants, which confirmed AD diagnosis based on amyloid-beta and neurofibrillary tangle pathology. Three brains have been successfully fixed to visualize NGF, and they showed NGF expression in a relatively limited area close to the needle tract. Numerous cholinergic neurons were also positive for acetylcholinesterase, choline acetyltransferase (ChAT), neurotrophin

receptor p75, and NGF. Finally, neurons exposed to AAV2-NGF were larger than those distal to the NGF expression field, and those exposed neurons from injected participants were also larger than those from a comparable NBM region in control participants (Rafii et al. 2014).

In contrast to *in vivo* gene therapy where virus particles are delivered directly to the brain, cell-based therapies introduce reprogrammed cell lines or stem cells into the brain, either stereotactically or through a certain device. The International Neuroethics Society (INS) conference proceeding of Viaña, Illes, and Gilbert (2018) and the poster presented during such conference, both of which are incorporated in this chapter and can be found in pages 199 to 207, review and illustrate a number of cell implantation strategies being tested in people with AD.

One of the studies reviewed in the poster is that of Kim et al. (2015) where human umbilical cord blood mesenchymal stem cells (hUCB-MSCs) were stereotactically transplanted into the hippocampus and precuneus of people with AD, given that these are the regions where amyloid or neurofibrillary tangles start to accumulate. In this study, nine people with AD (MMSE of 10 to 23) received injections of MSCs on both sides of the hippocampus and in the right precuneus. Three of the nine participants received a dose of 3.0 x 10^6 cells, with 1.0 x 10^6 cells injected in each region, whereas the other six received double the dose (6.0 x 10^6 cells in total). Safety, clinical, and laboratory assessments were performed at baseline, in several time periods during and after the month following the surgery, and the latest, 24 months after injection of the hUCB-MSCs.

With regards to safety and feasibility, Kim et al. (2015) reported that the procedure was feasible, well-tolerated, and safe for the population they enrolled. None of the participants experienced fever or haemorrhage 24 hours post-injection. There were no severe adverse events experienced; however, a number of participants had gastrointestinal disorders (nausea, colonic polyp, and/or vomiting), procedural complications (wound pain and/or ligament sprain), nervous system disorders (headache and/or dizziness), mild delirium, back pain, and/or asthenia (weakness or lack of energy) within three months after surgery. The authors deemed these events as surgery-related rather than stem cell-related events. No adverse events were observed during the 24-month extended follow-up study. Neurological assessment through MRI at 3 and 24 months revealed no tumour or subdural haemorrhages. All trial participants were immunologically stable at 12 weeks and 12 months post-injection.

Clinical, psychiatric, and functional measures used to assess the effect of hUCB-MSCs effect on cognition included the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog), Seoul Instrumental Activities of Daily Living (S-IADL), the Mini-Mental State Examination (MMSE), and caregiver-administered neuropsychiatric inventory. The low-dose group had a much larger degree of mean worsening in cognition based on ADAS-Cog and MMSE scores from baseline to 2 years post-injection; however, considering the small sample size and large standard deviation that resulted to a degree of overlap in the range of observed changes, it would be difficult to conclude that participants who received a much higher dose had slower cognitive decline. In addition, Kim et al. (2015) pointed out that the rate of observed decline in MMSE in their study was much faster than in typical AD, and they attributed it to the recruitment of people with early-onset AD. In terms of the S-IADL, the low

dose group had a worse mean decrease in functional outcome than the high-dose group 24 months post-injection.

Kim et al. (2015) also reported that their neurological assessments on amyloid burden via ^{11}C-labeled Pittsburgh compound B (PiB) positron emission tomography (PET) (PiB-PET) did not reveal differences in amyloid burden between the left and right precuneus. Kim et al. (2015) mentioned that this observation did not replicate results from animal studies that show a reduction of $A\beta_{42}$ plaques in the hippocampus and other brain regions following injection of hUCB-MSCs (Kim et al. 2011).

The purpose of this section is not to review cell implantation and gene therapy studies on people with AD. This section also does not aim to provide a comprehensive reflection on the ethical issues raised by the methodologies and results of these trials, similar to what was performed in Chapters 4 to 6. Rather, it just shows that there are other studies involving other invasive neurotechnologies on people with AD and that the ethical framework used to identify salient considerations can be used to analyse these other trials. In addition, some of the recommendations for improved participant protection and harm minimisation proposed in Chapters 4 to 6 can be translated to these trials.

As demonstrated in the abstract and shown in its accompanying poster that was presented at the 2017 INS meeting (pages 199 to 207), the selection criteria, informed consent procedure, trial design, and measured outcomes of cell implantation studies can be evaluated and compared, similar to what was performed in Chapters 4 and 5. From these comparisons, salient ethical concerns can be identified, especially with regards to the most

suitable population for this kind of intervention and the appropriate trial design (number of injection sites, dosage of injection) to minimise harms and to have a more equitable prospect of benefit for all participants involved. Although a portion of the ethical frameworks can be easily adapted to evaluate these studies, novel properties of the trials might also necessitate the examination of additional parameters for a more comprehensive ethical evaluation. For instance, given issues associated with ownership of biological material (Petrini 2012) and sourcing of stem cells (King & Perrin 2014), it is important to evaluate how the cells were obtained and the associated informed consent procedure. In addition, given that some trials did not directly introduce the cells into the brain, but rather introduced them via a reservoir that separates them from the brain environment and allows them to be explanted later on (Wahlberg et al. 2012), opens up discussions on the importance of reversibility of a procedure and its relation to informed consent and risks of harm.

The commentary of Viaña, Carter, and Gilbert (2018), presented in pages 193 to 198, also illustrates how a number of the recommendations made in Chapters 4 to 6 can be generalized to several invasive neurotechnological trials, including that of Rafii et al. (2014) and Kim et al. (2015). This paper highlights properties that are common to three types of invasive neurotechnological trials (DBS, cell implantation, and gene therapy) for AD, which include their partial or complete irreversibility, greater risks compared to observational studies or pharmacologic interventions, necessity of having another decision maker, and effects on relational adjustment and social positioning. Given these similar properties, recommendations relating to the informed consent process, translation from animal studies, assessment of capacity and role of the co-decision maker, and proper communication of the experimental nature of the trial and the extent of possible improvement from the

intervention can be applied to all three forms of invasive neurotechnologies being tested in people with AD.

As mentioned in the paragraphs discussing the conference abstract of Viaña, Illes, and Gilbert (2018) and in earlier discussions in this thesis, it is also important to acknowledge differences among the three technologies and incorporate knowledge on them in the refinement of existing ethical guidelines and in the formulation of additional ones. For example, whereas DBS is partially reversible and the device can be explanted (Gilbert 2015), stem cells and virus particles carrying a particular gene cannot be removed from the brain once they have been stereotactically injected, at least given the current state of technology. Once someone decides to participate in a cell implantation or *in vivo* gene therapy trial, their decision is binding for life. In contrast, for DBS, the trial participant and/or medical team can have the stimulation stopped or even have the device fully explanted. Although this could help reduce unwanted side effects and/or put a DBS recipient in a state where he or she could make competent decisions as in the case reported by Leentjens et al. (2004), this does not provide absolute guarantee of undoing all DBS-associated changes considering the initial lesioning process, stimulation-induced plasticity, and social attitudes towards DBS and/or neurological and psychiatric disorders that are beyond the medical team's control (Gilbert et al. 2017; Gilbert & Viaña 2018; Viaña & Gilbert 2018). In addition, the possibility of stopping the stimulation and/or explantation raises additional issues regarding decisional competence in later stages of dementia, considering the degenerative nature of AD, and on how much these decisions should be honoured should the recipient request for the device to be explanted.

Considering the funding being put by governments into AD research and the increasing number of people with AD in both developed and developing countries, along with the advancements in biotechnology and neuroscience, it is anticipated that more trials that necessitate stereotactic surgery and are potentially irreversible would be tested in people with AD. This emphasizes the need for bioethics to actively and continuously monitor existing studies and evaluate new ones. This section illustrates how the ethical frameworks used in Chapters 4, 5, and 6 and how a number of the ethical recommendations forwarded in these chapters can be used to assess and refine new invasive neurotechnological trials. It is crucial though to acknowledge differences among neurotechnologies and take these into account when translating ethical considerations and making certain recommendations.

The following publications have John Noel M. Viaña as the main author and thus, are included in this doctoral dissertation:

Pages 193 to 198:

Viaña, JNM, Carter, A & Gilbert, F 2018, 'Of Meatballs and Invasive Neurotechnological Trials: Additional Considerations for Complex Clinical Decisions', Originally published in the *American Journal of Bioethics Neuroscience* by the *Taylor & Francis Group*, vol. 9, no. 2, pp. 100-104. doi: 10.1080/21507740.2018.1460417. Available from: https://www.tandfonline.com/doi/abs/10.1080/21507740.2018.1460417

Pages 199 to 207:

Viaña, JNM, Illes, J & Gilbert, F 2018, 'Ethical Considerations for Cell Implantation in Alzheimer's Disease - Selected Abstracts From the 2017 International Neuroethics Society Annual Meeting', Originally published in the *American Journal of Bioethics Neuroscience* by the *Taylor & Francis Group*, vol. 9, no. 1, pp. W9-W10. doi: 10.1080/21507740.2018.1433731. Available from: https://www.tandfonline.com/doi/abs/10.1080/21507740.2018.1433731

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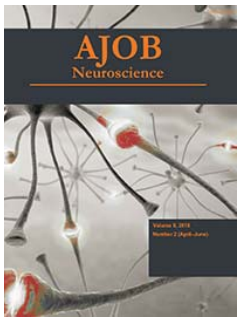

AJOB Neuroscience

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Of Meatballs And Invasive Neurotechnological Trials: Additional Considerations for Complex Clinical Decisions

John Noel M. Viaña, Adrian Carter & Frederic Gilbert

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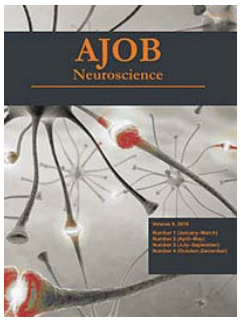
To link to this article: https://doi.org/10.1080/21507740.2018.1460417

Published online: 05 Jun 2018.



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Selected Abstracts From the 2017 International Neuroethics Society Annual Meeting

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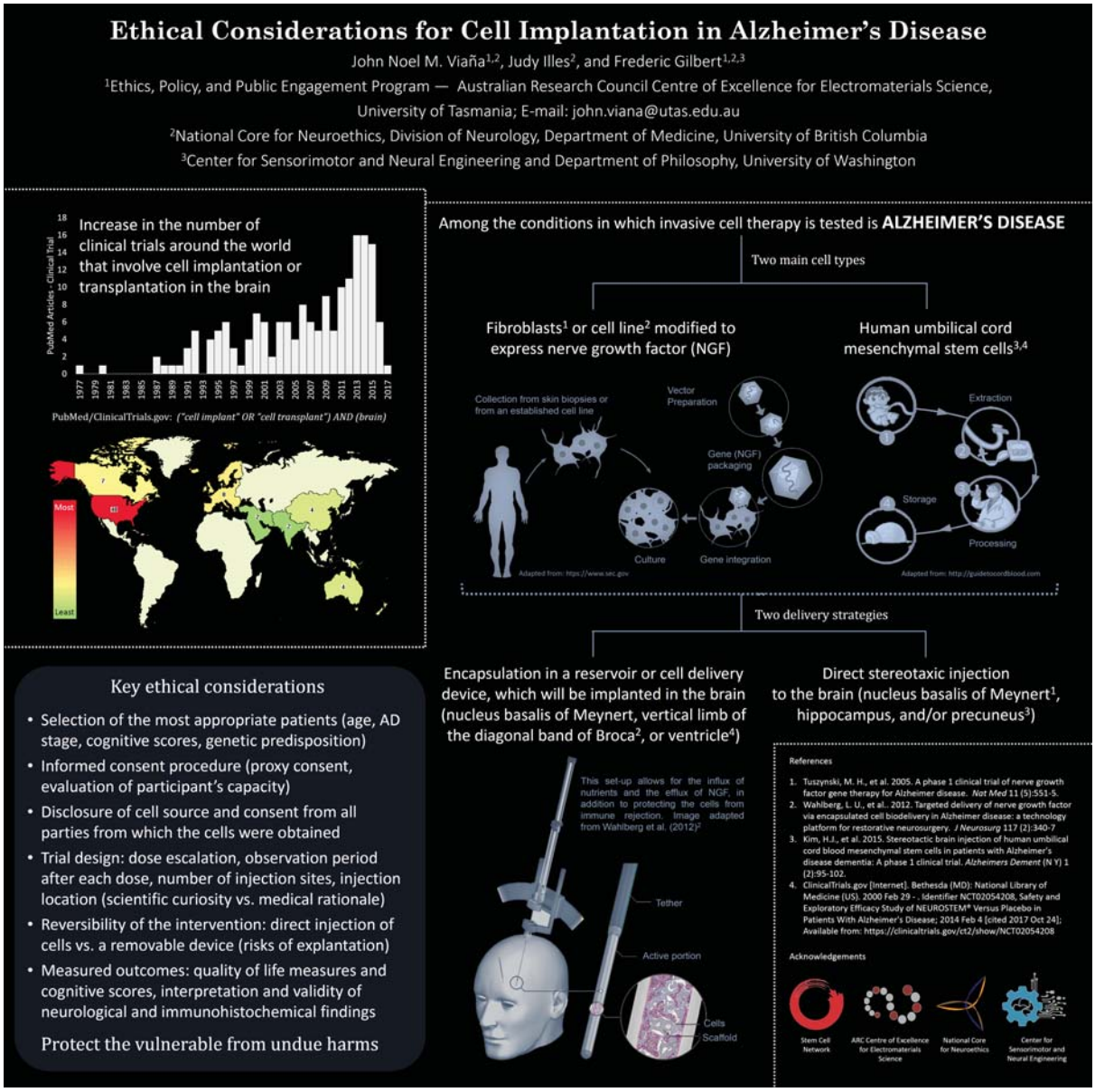
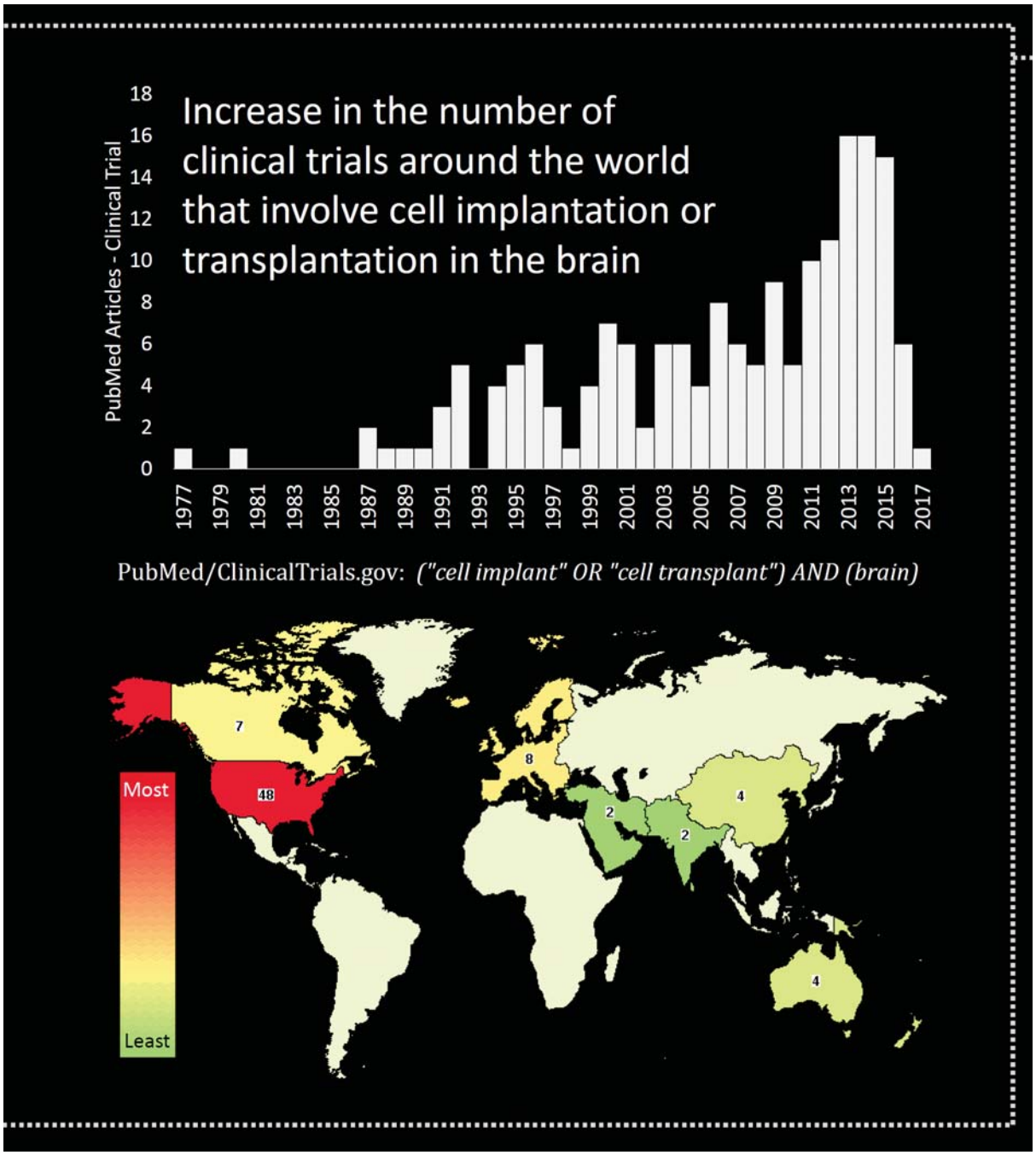
To link to this article: https://doi.org/10.1080/21507740.2018.1433731

Published online: 09 Mar 2018.

Full poster presented at the 2017 International Neuroethics Society meeting



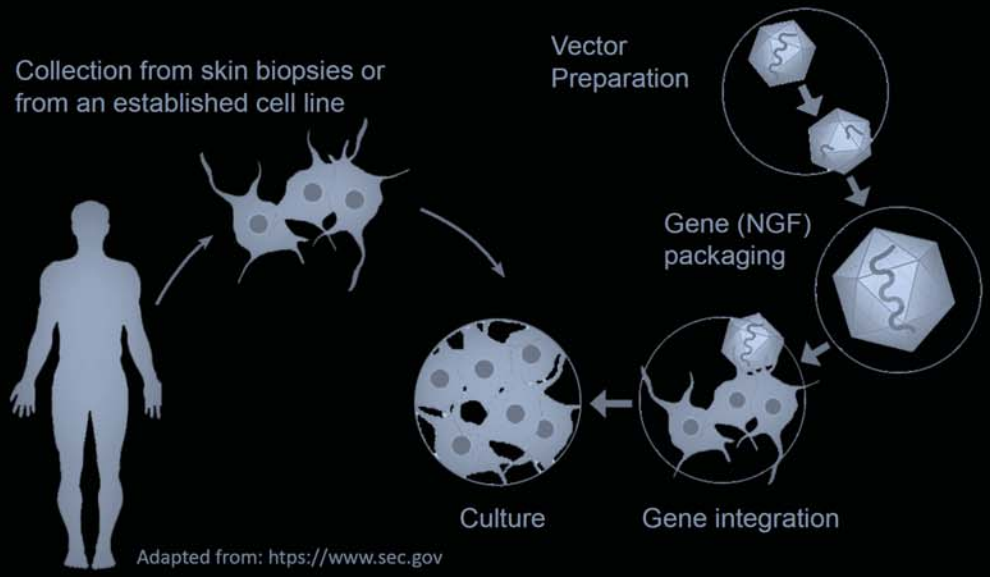
Part 1 of 4


Increase in the number of clinical trials around the world that involve cell implantation or transplantation in the brain
PubMed Articles - Clinical Trial
0
2
4
6
8
10
12
14
16
18
1977
1979
1981
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
2009
2011
2013
2015
2017
PubMed/ClinicalTrials.gov: ("cell implant" OR "cell transplant") AND (brain)
Most
Least
7
48
8
2
2
4
4

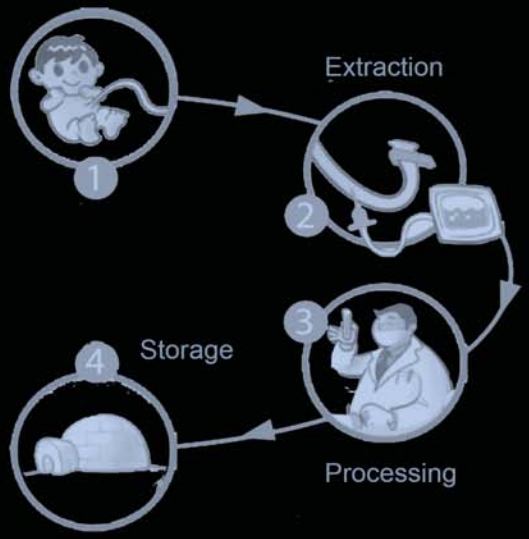
Among the conditions in which invasive cell therapy is tested is **ALZHEIMER'S DISEASE**

Two main cell types

Fibroblasts[1] or cell line[2] modified to express nerve growth factor (NGF)



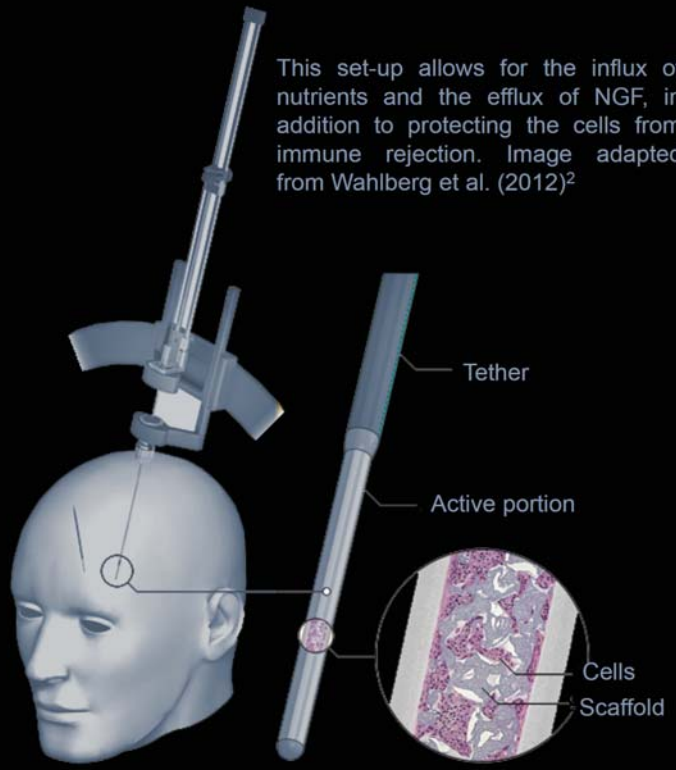
Human umbilical cord mesenchymal stem cells[3,4]



Two delivery strategies

Two delivery strategies

Encapsulation in a reservoir or cell delivery device, which will be implanted in the brain (nucleus basalis of Meynert, vertical limb of the diagonal band of Broca[2], or ventricle[4])



This set-up allows for the influx of nutrients and the efflux of NGF, in addition to protecting the cells from immune rejection. Image adapted from Wahlberg et al. (2012)[2]

Direct stereotaxic injection to the brain (nucleus basalis of Meynert[1], hippocampus, and/or precuneus[3])

References

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3. Kim, H.J., et al. 2015. Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: A phase 1 clinical trial. *Alzheimers Dement* (N Y) 1 (2):95-102.
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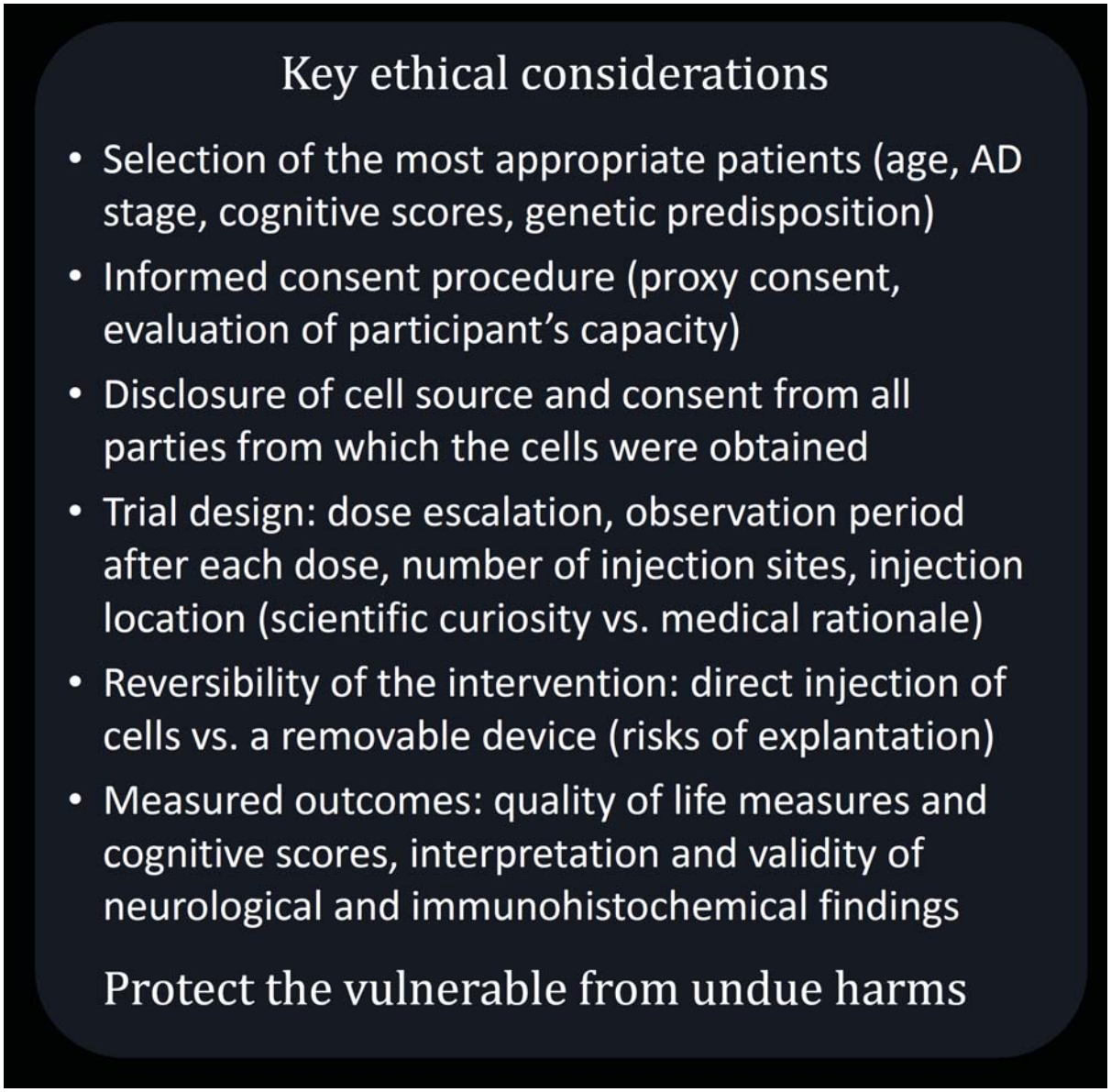
Center for Sensorimotor and Neural Engineering

Part 4 of 4


Key ethical considerations
• Selection of the most appropriate patients (age, AD stage, cognitive scores, genetic predisposition)
• Informed consent procedure (proxy consent, evaluation of participant's capacity)
• Disclosure of cell source and consent from all parties from which the cells were obtained
• Trial design: dose escalation, observation period after each dose, number of injection sites, injection location (scientific curiosity vs. medical rationale)
• Reversibility of the intervention: direct injection of cells vs. a removable device (risks of explantation)
• Measured outcomes: quality of life measures and cognitive scores, interpretation and validity of neurological and immunohistochemical findings
Protect the vulnerable from undue harms

III. Broadening the Neuroethical Oversight: Insights from Other Bioethics Publications

Considering the interdisciplinarity of neuroethics and the multiple levels of organisation in which ethical issues can be examined, the reflections in the papers presented in Chapters 3 to 7 can be seen as only few of the many ways to approach the ethical discourse on the topic of invasive neurotechnologies for Alzheimer's disease. There are definitely additional angles and more methodologies and frameworks from which the ethical considerations can be dissected and discussed.

Throughout my doctoral research, ethical issues on other biotechnological and neuroscientific products and projects have been explored. These include societal implications of findings from genomic research (Viaña, Bueno & Gilbert 2017); media portrayals of 3D bioprinting (Gilbert et al. 2018); public communication of the goals of the Human Brain Project (Viaña & Gilbert 2016); effect of a brain tumor on moral responsibility (Gilbert, Vranic & Viaña 2016); and eligibility, applicability and reliability issues on the use of decoded neurofeedback for psychiatric disorders (Viaña et al. 2016). Although the main discussion on these publications might not be directly related to the use of invasive neurotechnologies in people with AD, a few of the insights and angles from which the ethical concerns were identified can be translated to future studies on the ethics of invasive neurotechnologies for AD. Given that I have led or partook in the writing of these publications, they will be incorporated in this thesis. In this section, a brief discussion on each of these publications will be made, focusing on what aspects, methods, or frameworks can be translated to further explorations on ethical, legal, and societal issues on the use of DBS and other emerging invasive neurotechnologies in the management and treatment of people with AD and/or other forms of dementia.

In the commentary on the translation of outcomes from genomic research into clinical and public health contexts, which can be accessed in pages 219 to 222, Viaña, Bueno, and Gilbert (2017) responded to some of the claims made by Kong, Dunn, and Parker (2017) on how genomic research might lead to a sense of prognostic pessimism and on how it might draw the focus towards pharmacologic interventions and away from behavioural and environmental treatments. Using results from genome-wide association studies (GWAS) and functional genomics studies on bipolar disorder (BD), Viaña, Bueno, and Gilbert (2017) illustrated additional ways in which knowledge from GWAS can be used to better model and understand diseases. In order to demonstrate how genomic research might not necessarily lead to prognostic pessimism, we emphasized that results from GWAS on BD reveal that intrinsic biogenetic factors play a small role on BD progression, and that knowledge from genomic studies can actually help provide more personalized treatments, which can improve disease management. We also provided examples on how genomic research can reveal the influence of having particular genotypes on response to behavioural interventions and the effects of developmental stressors, both of which could help optimize behavioural therapies and encourage funding towards social interventions. Finally, we emphasized the importance of genetic counselling in order to minimize prognostic pessimism and provide advice to people on the management of their disease, especially on which interventions might be more effective given their genetic profile.

Some of the points raised in the paper of Viaña, Bueno, and Gilbert (2017) resonate with the ones forwarded in Chapter 5 (Viaña, Bittlinger & Gilbert 2017), especially on the importance of pre- and post-test genetic counselling for trials in which genetic data will be obtained from participants. Viaña, Bittlinger, and Gilbert (2017) also recommended several

modifications on the protocols and recruitment criteria of DBS for AD trials to account for differences between autosomal dominant early-onset AD and normal late-onset AD on disease progression, similar to the way the commentary (Viaña, Bueno & Gilbert 2017) provided examples on how genetic data can be used to refine pharmacologic and/or behavioural interventions. With new data coming from genetic and genomic studies on people with AD (Lambert et al. 2013; Chauhan et al. 2015; Escott-Price et al. 2015; Cuyvers & Sleegers 2016), it is important to consider how knowledge from these could help inform the possible response of different sub-groups of people with AD to invasive neurotechnological interventions. Although there might not be a direct genetically attributable influence on response to an invasive neurotechnological intervention, the effect of particular polymorphisms, copy number variations, or gene variants (Hooli et al. 2014; Zheng et al. 2015; Cuyvers & Sleegers 2016) on disease progression or on the symptoms that people with AD could experience could help tailor clinical trial protocols to ensure adequate monitoring and to minimise adverse events that could reduce the quality of life and cause distress to people who will also be subjected to an invasive neurological procedure.

The communication of scientific results to the public via mass media plays a pivotal role not only in keeping the public updated on the latest scientific discoveries and innovation, but also in helping people with certain disorders or diseases find clinical trials to improve their condition and/or address symptoms not remedied by approved therapy. Gilbert et al. (2018), whose paper is in pages 223 to 231, explores portrayals of 3D bioprinting in mass media that are indexed in the Factiva database. Articles were analysed to determine whether they include a patient story, mention risks and associated ethical issues, describe 3D bioprinting as a revolutionary technology, alludes to the printing of organs, and/or has an overall positive

portrayal of the technology. The analysis showed that most media articles positively portray 3D bioprinting and only very few mention risks and ethical issues. Almost a third of the articles also allude to the possibility of printing organs in the near future. In this manuscript, we emphasize the importance of balanced communication of the technology, ensuring that risks and ethical concerns are also disseminated. Hopefully, a more balanced and not positively overhyped representation of 3D-bioprinted materials and other technologies would avert incidences like the Macchiarini scandal where a number of people implanted with a biofabricated trachea died (Gilbert et al. 2018).

Balanced and accurate media reports are advocated for in the communication of the results of invasive neurotechnological trials for AD. Considering that there has already been positive media coverage on DBS for AD and its potential implications on boosting memory since 2011 (Gilbert & Dodds 2013; Gilbert & Ovadia 2011), it would be interesting and important to have an up-to-date evaluation of media portrayals of invasive neuroethologies for AD using the framework and methodologies by Gilbert et al. (2018). With the growing influence of social media, it would also be an important direction for future research to evaluate the portrayal of invasive neurotechnologies and discussions surrounding them on Facebook, Twitter, and other social media platforms (Purcell-Davis 2013; Kamenova, Reshef & Caulfield 2014; Robillard et al. 2015). These investigations would help determine whether there are unrealistic reports on the benefits and risks of these interventions, and also appraise current public perceptions and opinions on media reports of invasive neurotechnological trials for AD. Knowledge from these media studies could then be used by clinicians, clinical trial teams, and patient advocacy groups to devise strategies for more accurate depiction of these invasive neurotechnologies in medical consultations or in informed consent procedures,

with the ultimate goal of better informing people interested in participating in clinical trials and for those who will eventually enrol, prevent therapeutic misconception that can lead to unrealistic expectations (Lidz & Appelbaum 2002).

Aside from mass media outlets, it is also important for researchers, the institutions they are affiliated with, and funding bodies to properly and realistically communicate the objectives of their research and its deliverables upon completion. This would ensure that the public would not have overhyped expectations, which could undermine trust in science when they are not met. The commentary of Viaña and Gilbert (2016), which is in pages 232 to 235, evaluates the way that the Human Brain Project (HBP) is presented to the public by comparing it to the Human Genome Project (HGP), another large-scale biology project, and to the Blue Brain Project (BBP), which is the HBP's precursor. This paper emphasizes that although the HGP has been successful in its scientific goal of generating the sequence of the human genome, it has not lived up to predictions on it revolutionizing personalized medicine or ending diseases such as cancer and AD. Similarly, the BBP has also achieved its main scientific goal of digitally reconstructing a rat's somatosensory cortex (Markram et al. 2015); however, it has not really shown how this reconstruction can lead to therapies and treatments for neurological disorders, as promoted in its initial description (Markram 2006). Looking at the proposals made and final outputs of the BBP and HGP, this commentary underscores the need for the HBP to be more modest on its claims and more transparent on its limitations. The same recommendation applies to the centres, scientists, and doctors performing studies on invasive neurotechnologies for dementia. It is important for them to be realistic in their declarations and projections so as not to create false hope onto people with AD. A possible bioethical research project concerning this topic would be to examine review papers by

people involved in clinical trials of invasive neurotechnologies for AD, along with university press releases and interviews, to determine how they conveyed the goals of these trials to the public and whether these have been met upon the conclusion of the trial.

As mentioned in earlier chapters, it has been suggested that DBS has a putative effect on personality and may even result to disinhibition, hypersexuality (Akakin et al. 2014; Gilbert & Viana 2018), agitation (Rose et al. 2011), and aggressive behaviour (Papuc et al. 2015) in some individuals. People with dementia, especially those with frontotemporal dementia, may also exhibit socially undesirable, violent, and sexually disinhibited behaviours (Mychack et al. 2001; Kim et al. 2011; Cipriani et al. 2016). These DBS and/or AD-induced dramatic changes in mental states, personality, disposition, beliefs, and behaviour could lead to changes in personhood and identity, which would have implications on the responsibility of individuals with AD and/or receiving DBS over the conduct of their actions (Glannon 1998). Thus, it would be an interesting direction for future studies on the legal and societal issues raised by DBS and other invasive neurotechnologies for people with dementia to determine whether recipients of these technologies who also have AD would be morally responsible and culpable for crimes that they may commit.

The commentary of Gilbert, Vranic and Viaña (2016), presented in pages 236 to 239, reflects on the case of a person with a brain tumour who was sentenced to prison for sexual harassment and sexual assault of his pubescent stepdaughter. This paper questions the degree to which the man is accountable for his actions as a result of the tumour and the extent to which the man should be punished, along with issues on whether it would be ethically acceptable or required to use brain surgery to restore his capacities to allow him to

serve his sentence. Although there are differences in the pathology of a brain tumour with that of AD or other causes of dementia, the philosophical reflection in this commentary could be used in future inquiries on the sentencing of people with dementia (Doron et al. 2017). Having a brain implant, which could also lead to aggressive, violent, hypersexual, and socially deviant behaviours (Müller, Walter & Christen 2014), further complicates the issue, especially if the person no longer has adequate capacity to decide on the adjustment of parameters or on the implant's explantation. This implies that certain psychological screening procedures might have to be employed during participant selection to exclude people with a high risk of pedophilia or sexual deviancy from receiving an intervention that could increase the risk of conducting a harmful sexual act (Müller, Walter & Christen 2014). The need to reflect on these issues from philosophical, medical, legal, and sociological perspectives would be more pressing in the years to come given the increasing number of people with dementia who have received or will be receiving an invasive neurotechnology (Viaña, Carter & Gilbert 2018).

The last manuscript that is included in this section is that of Viaña et al. (2016), presented in pages 240 to 243, which discusses eligibility, applicability, and reliability issues on the use of decoded neurofeedback (dNF) in people who have schizophrenia or major depressive disorder (MDD). This commentary reviews studies involving people with MDD or schizophrenia who participated in sessions of real-time fMRI neurofeedback (rtfMRI-NF) wherein representations of real time-reported brain activity patterns are used by patients to learn self-regulation in order to change behaviour (Stoeckel et al. 2014). From the results of the studies reviewed, Viaña et al. (2016) pointed out salient ethical issues that might arise from clinical applications of decoded neurofeedback, a more computationally advanced version of rtfMRI-NF. Salient ethical concerns include accurately determining the people who

would benefit from dNF given the variability in MDD and schizophrenia symptomatology and inability of certain patients to focus on the learning task, and ensuring that people with MDD or schizophrenia would be able to translate self-regulation strategies they learned in the lab to real-life scenarios such as when hallucinations or suicidal tendencies arise.

Although there are key differences between dNF and invasive neurotechnologies such as DBS, gene therapy, and stem cells, especially with regards to safety and reversibility, the framework used in this commentary would still be translatable. As highlighted in the selection criteria sections of Chapters 4 (Viaña et al. 2017) and 5 (Viaña, Bittlinger & Gilbert 2017), it is important to evaluate whether a technology is applicable for certain sub-populations, considering symptomatic variabilities. Careful identification of relevant eligibility criteria is of utmost importance, especially in procedures wherein participants will be subjected to stereotactic surgery and general anaesthesia (Viaña, Carter & Gilbert 2018). Although the reliability parameter might not be fully applicable to invasive neurotechnologies covered in this thesis given that they generally function independently of the recipient's effort (due to the invasive neurotechnology being physically part of and continuously exerting its effects on the recipient), issues of reliability could arise in newer versions of invasive neurotechnologies such as closed-loop DBS systems (Senova, Chaillet & Lozano 2018). With closed-loop DBS systems, it is important for the mathematical models and software to be reliable enough to stimulate only when necessary and ensure that the stimulation provided would not lead to disruption of network activity crucial to memory formation and retrieval. Examining the ethics of closed loop stimulation systems is beyond the scope of this thesis; however, it would definitely be an important subject for future bioethical explorations, particularly on concerns regarding eligibility, applicability, and reliability.

From genomic research (Viaña, Bueno & Gilbert 2017) to 3D bioprinting (Gilbert et al. 2018) to decoded neurofeedback (Viaña et al. 2016), this section covers a wide range of neuro- and biotechnological products and/or endeavours that necessitate ethical scrutiny. By showing how the ethical issues raised and methodologies used in the different publications included relate to invasive neurotechnologies for dementia, this dissertation shows how integrated and interdisciplinary neuroethics is as a discipline. It also illustrates how frameworks from other studies can be adapted and refined to identify ethical concerns in a different technology. Finally, this section suggests directions and topics for future conceptual and empirical research that need to be undertaken to ensure that ethical reflection on invasive neurotechnologies for dementia keeps up with technological innovation. As neuroscience continues to progress and new technologies are being tested in humans, viewing issues in more levels of organisation or through additional disciplinary lenses, in line with pragmatism's advocacy for interdisciplinarity (Fins, Bacchetta & Miller 1997; Racine 2008b), would facilitate a richer and more comprehensive bioethical discussion.

The following publications have John Noel M. Viaña as the main author or as a co-author and thus, are included in this doctoral dissertation:

Pages 219 to 222:

Viaña, JNM, Bueno, RJ & Gilbert, F 2017, 'Beyond Genomic Association: Ethical Implications of Elucidating Disease Mechanisms and Genotype-Influenced Treatment Response', Originally published in the *American Journal of Bioethics* by the *Taylor & Francis Group*, vol. 17, no. 4, pp. 24-26. doi: 10.1080/15265161.2017.1284931. Available from: https://www.tandfonline.com/doi/full/10.1080/15265161.2017.1284931

Pages 223 to 231:

Gilbert, F, **Viaña, JNM**, O'Connell, CD & Dodds, S 2018, 'Enthusiastic portrayal of 3D bioprinting in the media: Ethical side effects', Originally published in *Bioethics* by *John Wiley & Sons, Inc*, vol. 32, no. 2, pp. 94-102. doi: 10.1111/bioe.12414. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bioe.12414

Pages 232 to 235:

Viaña, JNM & Gilbert, F 2016, 'Big Explanations for Big Expectations: Deriving Lessons from the Human Genome and Blue Brain Projects', Originally published in the *American Journal of Bioethics Neuroscience* by the *Taylor & Francis Group*, vol. 7, no. 1, pp. 18-20. doi: 10.1080/21507740.2016.1138154. Available from: https://www.tandfonline.com/doi/full/10.1080/21507740.2016.1138154

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Pages 236 to 239:

Gilbert, F, Vranic, A & **Viaña, JNM** 2016, 'Acquired Pedophilia and Moral Responsibility', Originally published in the *American Journal of Bioethics Neuroscience* by the *Taylor & Francis Group,* vol. 7, no. 4, pp. 209-211. doi: 10.1080/21507740.2016.1244221. Available from: https://www.tandfonline.com/doi/full/10.1080/21507740.2016.1244221

Pages 240 to 243:

Viaña, JNM, Freitas, L, Severo, MC & Gilbert, F 2016, 'Decoded Neurofeedback: Eligibility, Applicability, and Reliability Issues for Use in Schizophrenia and Major Depressive Disorder', Originally published in the *American Journal of Bioethics Neuroscience* by the *Taylor & Francis Group*, vol. 7, no. 2, pp. 127-129. doi: 10.1080/21507740.2016.1190422. Available from: https://www.tandfonline.com/doi/full/10.1080/21507740.2016.1190422

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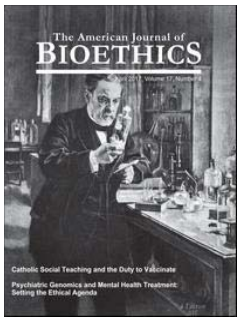

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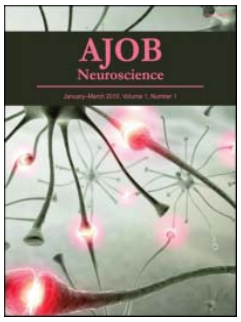

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Acquired Pedophilia and Moral Responsibility

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Decoded Neurofeedback: Eligibility, Applicability, and Reliability Issues for Use in Schizophrenia and Major Depressive Disorder

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Chapter Eight. Concluding Remarks

From genes, molecules, and cells that make up the brain and maintain its proper function to synapses and networks the give rise to consciousness, cognition, and behaviour, the study of neuroscience encompasses multiple levels of biological organisation. As illustrated throughout this dissertation, both Alzheimer's disease and deep brain stimulation exert their effect on several levels, ultimately leading to what can be observed in a person with AD or in someone receiving DBS therapy. However, simply reducing the lived experience of a person with AD and/or undergoing DBS to pathological hallmarks and to alterations in neural firing limits understanding of the true scope of the disease and of this intervention. People are not isolated entities solely defined by their neurological make up; on the other hand, they are embodied beings living in a particular society and have relationships with other members of it. As such, DBS for AD may aggravate existing or even introduce new vulnerabilities, manifested both through the effects of the intervention on the pathology and the person; on his or her relationships with family, caregivers, and society members; and on his or her social position and care arrangements or context (Dodds 2005, 2007, 2013). Understanding the extent to which a disease affects an individual and how novel therapies being tested might improve or worsen his or her lived experience requires examination that does not only utilise concepts and tools from neuropathology, neurology, and psychiatry, but also acknowledges the contribution of social psychology, philosophy, sociology, and medical humanities.

By seeing people with AD who participate in DBS trials as having brains affected by the pathology, surgery, and stimulation, the totality of which reflected in their cognition and mental states; and as persons who are embodied, relational, and social beings, this thesis highlights the ethical challenges that arise from clinical trials of DBS on people with AD. This thesis mainly employs a pragmatic ethical approach (Fins, Bacchetta & Miller 1997; Racine 2008b), indirectly drawing from the principles of respect for persons, beneficence, non-maleficence, and justice (Beauchamp & Childress 2013) and from frameworks in research ethics (Emanuel, Wendler & Grady 2000; Li et al. 2016), to examine clinical trial protocols of DBS and other invasive neurotechnological trials for AD and determine aspects that could be further improved to promote participant welfare. Extensive philosophical grounding of these principles and of other approaches to ethical reasoning are already widely presented in the theoretical bioethics literature, and as such, this thesis aims to focus the discussion on the ethical issues directly related to the medical and research domains. Considering the increasing burden of AD and the technological innovations that facilitate several new interventions to be better developed and even tested in humans, there is an ever pressing need to raise and deliberate on ethical issues in a manner directly relevant to the clinical trials; using a language that doctors, scientists, and participants can relate to; and sharing concerns in journals that medical and health practitioners mainly subscribe to.

The three main publications comprising this thesis employ a pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) to determine ethical issues from the perspective of the effects of DBS for AD on the brain and person and its possible repercussions to relationships and society. These publications aim to provide an overview on clinical trials and animal studies on DBS for AD; determine ethical issues that arise from the protocols of the

studies that were reviewed; and propose recommendations to address them. These publications also aim to demonstrate how examining issues through different levels and lenses can lead to recommendations that have a direct influence on the way that current and/or future trials are conducted – from pointing out issues in the translation of DBS for AD from animal models to the first participants to different sub-populations (Viaña et al. 2017); to underscoring how genetic risk factors might affect DBS outcome and how should clinical trials account for this (Viaña, Bittlinger & Gilbert 2017); and finally, to utilising information and interpretations from studies on the effects of AD on selfhood and DBS on outlook, behaviour, personality, and relationality (Gilbert et al. 2017; Gilbert & Viaña 2018; Gilbert, Viaña & Ineichen 2018) in anticipating and mitigating possible adverse immediate, short-term, and long-term effects of DBS for AD (Viaña & Gilbert 2018).

In addition to DBS, other neurotechnologies such as cell implantation and gene therapy are also being investigated for AD. The trial-focused and application-oriented grounding of ethical recommendations on DBS for AD in this thesis can be used to evaluate trials on other invasive neurotechnologies and propose recommendations on trial protocols that directly address associated ethical concerns (Viaña, Carter & Gilbert 2018; Viaña, Illes & Gilbert 2018). Further down the track, the ethical examination of DBS for AD can be extended to not only analyse and propose recommendations for pre-clinical studies and in-human trials, but also assess media depictions of this topic, promotion of this line of research, and its implications on legal culpability and moral responsibility (Gilbert et al. 2018; Gilbert, Vranic & Viaña 2016; Viaña & Gilbert 2016). Ethical examination should also keep track with innovations on neurotechnologies and discoveries on the biology of AD, refining recommendations when necessary to account for additional complexities (Viaña, Bueno &

Gilbert 2017; Viaña et al. 2016) and to ensure that the recommendations made are properly grounded in medical and scientific realities.

This dissertation draws insights from pragmatism (Fins, Bacchetta & Miller 1997; Racine 2008b) in order to propose recommendations that aim to improve the ethical conduct of clinical trials of DBS and other invasive neurotechnologies in people with AD. Although ethical reflection in this dissertation is based on empirical information from the results of DBS for AD clinical trials, animal studies evaluating the effects of fornix stimulation, studies on the impact of AD on selfhood, and information from research involving people who have received DBS for other conditions, the major limitation of this work is that there was no direct engagement with people with AD who have received DBS, their caregivers and/or family members, and researchers and health care personnel conducting the trials. As such, this thesis can only claim partial application of a pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b), considering the absence of engagement, deliberation, and negotiation with key stakeholders involved in this clinical research endeavour.

To gauge the full spectrum of ethical concerns arising from clinical trials of DBS for AD, qualitative and quantitative studies must be performed on people with AD who have received or will receive DBS and their family members, caregivers, study partners, and/or surrogate decision makers, inquiring about their motivations and apprehensions for participating in a clinical trial; lived experience before, during, and after a DBS trial; and ethical and moral concerns faced during different trial stages. Interviews and surveys with researchers, scientists, doctors, and other medical professionals who are conducting DBS for AD trials and/or are involved in laboratory research relevant to this topic should also be performed.

This will be crucial in acquiring a fuller understanding of the state of knowledge and research in this field; preliminary evidence on the potential safety and efficacy of DBS for AD beyond what is available in academic publications; motivations for pursuing this line of work in a vulnerable population, despite limited evidence; factors and considerations undertaken in participant recruitment, trial design, and selection of outcome measures; and personal reflection on possible ethical issues arising from the conduct of these clinical trials. To incorporate negotiation and deliberation (Fins, Bacchetta & Miller 1997; Racine 2008b), focus groups involving various stakeholders can be facilitated, allowing joint discussion on ethical issues from multiple perspectives and collaborative decision-making on possible ways in which they can be addressed. In these studies, a hypothesis-based approach could also be employed to determine how certain factors such as decision-making capacity of people with AD and their family members and possible conflicts of interest of researchers could influence their perceptions of ethical dilemmas and moral concerns arising from DBS for AD trials. Empirical studies are of crucial importance in this line of research, building upon the conceptual work presented in this dissertation. They would also provide an excellent opportunity to gauge whether the concerns and recommendations forwarded in the incorporated publications are similar to the ones voiced out by various parties, and on how can the recommendations be further improved to acknowledge contextual variations and the perspectives of multiple stakeholders.

Although most publications presented in this dissertation performed a systematic search using specific keywords on various databases to survey empirical studies relevant to understanding ethical concerns in clinical trials of invasive neurotechnologies in people with AD, a more systematic review methodology following the PRISMA-P statement (Shamseer et

al. 2015) could have been employed. This would facilitate increased transparency on the selection of animal studies, clinical trials on DBS for AD, and other empirical studies on people with AD or DBS recipients that are included in the publications and used to derive ethical recommendations. Furthermore, future ethics research on this topic could formulate and utilise a more concrete protocol in determining which occurrences during a clinical trial warrant serious consideration and an actual ethical recommendation. For the three main publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) in this dissertation, the requirements for ethical research trial forwarded by Emmanuel, Wendler, and Grady (2000) and elements essential in an ethics section of a clinical trial protocol, identified by Li et al. (2016), were used to direct the focus of the ethical analysis to participant selection, study design, and outcome measurement and reporting. In line with a pragmatic approach to bioethical analysis (Fins, Bacchetta & Miller 1997; Racine 2008b), deliberation with people with AD, family members, and healthcare personnel should be employed to determine what aspects in a DBS for AD clinical trial do they deem highly important and what results from previous studies would warrant more serious ethical reflection.

Overall, this dissertation focuses on the "ethics of neuroscience" while ensuring that the "neuroscience in ethics" is not put to the sideline by grounding ethical reflection on empirical data from animal studies, clinical trials, and other quantitative and qualitative research on people with AD and/or undergoing DBS, and by proposing recommendations directly addressing clinical trial procedures. Ethics can help direct neuroscience towards a more humane future, emphasizing the shared importance and relevance of the brain, mind, and society in defining a person and his/her actions. On a similar light, neuroscience can also help produce a more relatable ethics, ensuring that recommendations made are practical and

could actually benefit and protect the people that it primarily advocates for. As with different disciplines going hand-in-hand to better understand AD and DBS and to frame the discourse in this manuscript, neuroethicists, neuroscientists, and most importantly, neuro-recipients should engage in dialogue and collaboration to create a balanced future for neurotechnology development, one that realizes how neurotechnologies can dramatically improve lives of people but also acknowledges that in the absence of proper scrutiny and reflection, how they can impair individuals and make them lose trust in the enterprise of neuroscience and the exercise of neuroethics.

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Note: References that have already been properly cited and referenced in the published articles are not included in this section, unless they have been cited again in the text of this dissertation.

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APPENDICES

Appendix 1. Statement of Co-Authorship

The following people and institutions contributed to the publication of work undertaken as part of this thesis:

Candidate	John Noel M. Viaña; Philosophy and Gender Studies Program, School of Humanities, College of Arts, Law, and Education, University of Tasmania
Author 1	Frederic Gilbert; University of Tasmania and University of Washington; PhD supervisor
Author 2	Susan Dodds; University of New South Wales and University of Tasmania; PhD co-supervisor
Author 3	Merlin Bittlinger; Charité Universitätsmedizin Berlin
Author 4	Roemel Jeusep Bueno; Charité Universitätsmedizin Berlin and University of the Philippines Manila
Author 5	Adrian Carter; Monash University and University of Queensland
Author 6	Mark Cook; University of Melbourne
Author 7	Lorena Freitas; École Polytechnique Fédérale de Lausanne
Author 8	Eliza Goddard; University of Tasmania and University of New South Wales
Author 9	Malcolm Horne; University of Melbourne
Author 10	Judy Illes; University of British Columbia
Author 11	Cathal D. O'Connell; University of Melbourne
Author 12	Mario Carlo Severo; Ghent University
Author 13	James Vickers; University of Tasmania

Author 14	Andrej Vranic; Hôpital Européen de Paris and University Medical Centre Ljubljana
Author 15	Christian Ineichen; University of Zurich

Author details and their roles

(Papers are arranged alphabetically by author)

Paper 1, Gilbert F, **Viaña JNM**, O'Connell CD, Dodds S (2018) Enthusiastic portrayal of 3D bioprinting in the media: ethical side effects. Bioethics 32(2): 94-102.

Located in Chapter 7

Author 1 (Gilbert) was the primary author. He designed and conceptualized the research project, analysed the data, drafted majority of the paper, and critically revised it for publication.

Candidate (Viaña) was the second author. He contributed to the design and conception of the research project and drafted parts of the manuscript. He also surveyed medical and patent databases and bioethics journals, analysed a portion of the media articles, interpreted the data, and constructed the figures in this paper. Overall, he contributed to approximately 30% of the planning, execution, preparation, and revision of the manuscript.

Author 11 (O'Connell) contributed to the scientific content and discussion in this manuscript, drafted substantial parts of the paper, and took substantial part in its revision for publication.

Author 2 (Dodds) contributed to the conceptual discussion of project, drafted substantial portions of the manuscript, and took substantial part in its revision for publication.

Paper 2, Gilbert F, Goddard E, **Viaña JNM**, Carter A, Horne M (2017) I miss being me: phenomenological effects of deep brain stimulation. AJOB Neuroscience 8(2): 96-109.

Located in Chapter 3

Author 1 (Gilbert) was the primary author. He designed and conceptualized the research project, performed the interviews, analysed the qualitative data and grounded it in phenomenology, drafted majority of the paper, and critically revised it for publication.

Author 8 (Goddard) had significant contribution in the content of Table 2 in the paper, which presents various accounts or models of potential DBS-associated effects on autonomy, agency, selfhood, and identity. She also had key inputs in the philosophical discussions on self-estrangement and embodiment. She also assisted in data analysis and in the critical revision of the paper for publication.

Candidate (Viaña) contributed to the scientific and medical discussion on factors that might contribute to feelings of estrangement and changes in behaviour and self-concept during DBS therapy, highlighting the interaction between target region, stimulation parameters, medication changes, and neurodegenerative progression. He also helped in the proofreading and revision of the manuscript. Overall, his contribution amounts to 7.5% of the total work for this manuscript.

Author 5 (Carter) contributed to the discussion on the development of compulsive behaviours or impulse control disorders following dopamine replacement therapy, comparing it to what was observed in the patients undergoing DBS therapy who were interviewed.

Author 9 (Horne) contributed to the conception of the research project and facilitated the recruitment of patients for interview.

Paper 3, Gilbert F, Vranic A, **Viaña JNM** (2016). Acquired paedophilia and moral responsibility. AJOB Neuroscience 7(4): 209-11.

Located in Chapter 7

Author 1 (Gilbert) was the primary author. He reflected on the case and its associated ethical conundrums and implications, wrote majority of the commentary, and critically revised it for publication.

Author 14 (Vranic) contributed to the medical discussion and to the figure (MRI scan) presented in the commentary.

Candidate (Viaña) contributed to the neurobiological discussion on glioblastoma progression and its potential effects on behaviour depending on the brain region affected. He also helped in the proofreading and revision of the manuscript. Overall, his contribution amounted to 5% of the total work for this manuscript.

Paper 4, Gilbert F, **Viaña JNM** (2018). A personal narrative on living and dealing with psychiatric symptoms after DBS surgery. Narrative Inquiry in Bioethics 8(1): 67-77.

Located in Chapter 3

Author 1 (Gilbert) was the primary author. He designed and conceptualized the research project, conducted the initial and follow-up interviews, analysed the qualitative data and identified salient ethical issues, drafted majority of the paper, and critically revised it for publication.

Candidate (Viaña) contributed to the scientific and medical review and discussion on the potential psychiatric side effects of subthalamic nucleus deep brain stimulation in people with Parkinson's disease. He also provided inputs on the importance of patient narratives and perspectives in managing medical conditions and treatment response, in addition to informing other patients and their family the lived experience of those having a similar condition and/or undergoing a particular medical intervention. He also helped in the proofreading and critical revision of the manuscript. In total, his contribution amounted to 40% of the work for this manuscript.

Paper 5, Gilbert F, **Viaña JNM**, Ineichen C (2018) Deflating the BDBS causes personality changes bubble. Neuroethics. Article published online first on June 19, 2018. doi: 10.1007/s12152-018-9373-8. Available from: https://link.springer.com/article/10.1007%2Fs12152-018-9373-8

Located in Chapter 3

Author 1 (Gilbert) was the primary author. He designed and conceptualized the research project, analysed the data, drafted majority of the paper, and critically revised it for publication.

Candidate (Viaña) was the second author. He provided some inputs on the design of the research project and drafted parts of the manuscript. He also did the initial search in bioethics, medical, and scientific databases on deep brain stimulation and its possible effects on personality, identity, agency, authenticity, autonomy, and/or self (PIAAAS). He performed the initial screening of articles to identify relevant ones and exclude those that did not cover or only provided minimal discussion on the putative effects of DBS on PIAAAS. He also wrote parts of the Methods and Limitations sections and contributed to the labelling and design of the figures. Overall, he contributed to approximately 15% of the planning, execution, preparation, and revision of the manuscript.

Author 15 (Ineichen) contributed to the medical and scientific content and discussion in this manuscript, particularly on neuropsychiatric symptoms in Parkinson's disease and on the importance of case-control studies; drafted parts of the paper; and took significant part in its revision for publication.

Paper 6, Viaña JNM, Bittlinger M, Gilbert F (2017) Ethical considerations for deep brain stimulation trials in patients with early-onset Alzheimer's disease. Journal of Alzheimer's Disease 58(2): 289-301.

Located in Chapter 5

Candidate (Viaña) was the primary and corresponding author, and his contribution comprised 85% of the work for this manuscript. He was mainly responsible for conceptualising the main ideas for this project, organising the structure and flow of the paper, and writing majority of the text. He performed the literature review in scientific, medical, and ethical journals for information presented in this manuscript, especially regarding deep brain stimulation and early-onset Alzheimer's disease. He also filled in the data for, constructed, and formatted the tables and figures. He facilitated the revision of the manuscript, responded to the comments of the editor and reviewers, and carefully proofread it prior to final publication.

Author 3 (Bittlinger) contributed to the ideas and ethical considerations posited in this manuscript, especially in the "Considerations for patient selection" and "Interpretation and communication of study results" sections to which he also provided written text. He also provided critical feedback to other sections of the paper and helped ensure the accuracy of the information presented in the text and in the tables. He also helped fill in data for Table 1, where criteria for patient recruitment in studies on DBS for AD were presented. He also assisted in the critical revision of the manuscript.

Author 1 (Gilbert) contributed to the main idea for this publication, provided some inputs on the ethical discourse, and assisted in its critical revision for publication.

Paper 7, Viaña JNM, Bueno RJ, Gilbert F. (2017) Beyond Genomic Association: Ethical Implications of Elucidating Disease Mechanisms and Genotype-Influenced Treatment Response. The American Journal of Bioethics 17(4): 24-26.

Located in Chapter 7

Candidate (Viaña) was the primary and corresponding author, and his contribution comprised 85% of the work for this manuscript. He conceptualised the main idea for this paper, submitted a commentary proposal to the journal for consideration, and coordinated with the other authors for the structure and content of the final manuscript. He wrote majority of the paper and reviewed relevant literature on bipolar disorder and associated genetic and functional genomics studies for integration in the paper's ethical discussion. He also liaised with the editors and carefully proofread the paper prior to final publication.

Author 4 (Bueno) contributed to the discussion on genetic counselling, and he assisted in the critical revision of the manuscript, ensuring the scientific accuracy of the information presented in it.

Author 1 (Gilbert) contributed to the ethical discussion in this manuscript, relating previous work on the implications to patients of neurobiological explanations for sudden-onset psychiatric conditions. He also helped in the critical revision of the manuscript.

Paper 8, Viaña JNM, Carter A, Gilbert F (2018) Of Meatballs and Invasive Neurotechnological Trials: Additional Considerations for Complex Clinical Decisions. AJOB Neuroscience 9(2): 100-104.

Located in Chapter 7

Candidate (Viaña) was the primary and corresponding author, and his contribution comprised 95% of the work for this manuscript. He conceptualised the main idea for this paper, submitted a commentary proposal to the journal for consideration, and coordinated with the other authors for the structure and content of the final manuscript. He wrote majority of the paper, integrating previous work on the ethics of deep brain stimulation, stem cells, and gene therapy for Alzheimer's disease. He also gathered data on the number of studies involving invasive neurotechnologies for people with dementia and their estimated enrolment, and he constructed the graphs to portray clinical trial trends throughout the years. He also liaised with the editors and carefully proofread the paper prior to final publication.

Author 5 (Carter) contributed to the scientific and ethical discussion in this paper, helped clarify and better elaborate the ideas raised, and critically revised it prior to submission.

Author 1 (Gilbert) contributed to the scientific and ethical discussion in this paper, helped clarify and better elaborate the ideas raised, and critically revised it prior to submission.

Paper 9, Viaña JNM, Freitas L, Severo MC, Gilbert F (2016) Decoded Neurofeedback: Eligibility, Applicability, and Reliability Issues for Use in Schizophrenia and Major Depressive Disorder. AJOB Neuroscience 7(2): 127-129.

Located in Chapter 7

Candidate (Viaña) was the primary and corresponding author, and his contribution comprised 50% of the work for this manuscript. He conceptualised the main idea for this paper, submitted a commentary proposal to the journal for consideration, and coordinated with the other authors for the structure and content of the final manuscript. He came up with the three salient properties (eligibility, applicability, and reliability) that have to be evaluated for decoded neurofeedback's application to psychiatric disorders, and he wrote the introductory material for MRI, schizophrenia, and major depressive disorder. He also liaised with the editors and carefully proofread the paper prior to final publication.

Author 7 (Freitas) discussed eligibility, applicability, and reliability considerations for decoded neurofeedback's use in people with schizophrenia. She also helped clarify and better elaborate the ideas raised; and she took significant part in critically revising the paper prior to submission, ensuring the accuracy of the neuroscientific information presented.

Author 12 (Severo) discussed possible eligibility, applicability, and reliability issues for decoded neurofeedback's use in people with major depressive disorder. He also helped clarify and better elaborate the ideas raised; and he took significant part in critically revising the paper prior to submission, ensuring the accuracy of the neuroscientific information presented.

Author 1 (Gilbert) contributed to the scientific and ethical discussion in this paper, helped clarify and better elaborate the ideas raised, and critically revised the manuscript prior to submission.

Paper 10, Viaña JNM, Gilbert F (2016) Big Explanations for Big Expectations: Deriving Lessons from the Human Genome and Blue Brain Projects. AJOB Neuroscience 7(1): 18-20.

Located in Chapter 7

Candidate (Viaña) was the primary and corresponding author, and his contribution comprised 95% of the work for this manuscript. He conceptualised the main idea for this paper, submitted a commentary proposal to the journal for consideration, and coordinated with the second author for the structure and content of the final manuscript. He wrote majority of the paper, reviewing literature on the Human Brain Project (HBP), Human Genome Project (HGP), and Blue Brain Project (BBP) and reflecting on how the HGP and BBP can inform expectations from and publicity of the HBP. He also liaised with the editors and carefully proofread the paper prior to final publication.

Author 1 (Gilbert) contributed to the ethical discussion in this paper, helped clarify and better elaborate the ideas raised, and critically revised the manuscript prior to submission.

Paper 11, Viaña JNM, Gilbert F (2018) Deep brain stimulation for people with Alzheimer's disease: anticipating potential effects on the tripartite self. Dementia. Article first published online: March 11, 2018; https://doi.org/10.1177/1471301218761147

Located in Chapter 6

Candidate (Viaña) was the primary and corresponding author, and his contribution comprised 95% of the work for this manuscript. He conceptualised the main idea for this paper and coordinated with the second author for the structure and content of the final manuscript. He wrote majority of the paper, reviewing literature on the effects of Alzheimer's disease (AD) or deep brain stimulation (DBS) on identity and selfhood and using this information to anticipate potential effects of DBS on three aspects of the self of people with AD. He also formulated the ethical recommendations to ensure adequate consideration and proper management of the potential impacts of DBS on the selfhood of people with AD before and during the trial. He also liaised with the editors, responded to and addressed the reviewer's comments, and carefully proofread the paper prior to final publication.

Author 1 (Gilbert) contributed to the ethical discussion in this paper, especially in the section on "Ethical implications for consent and care"; helped clarify and better elaborate the ideas raised; and critically revised the manuscript prior to submission and final publication.

Paper 12, Viaña JNM, Illes J, Gilbert F (2018) Ethical Considerations for Cell Implantation in Alzheimer's Disease - Selected Abstracts From the 2017 International Neuroethics Society Annual Meeting. AJOB Neuroscience 9(1): W9-W10. https://doi.org/10.1080/21507740.2018.1433731.

Located in Chapter 7

Candidate (Viaña) was the primary and corresponding author, and his contribution comprised 90% of the work for the abstract and the poster presented at the 2017 International Neuroethics Society conference. He conceptualised the main idea for this presentation and coordinated with the other authors for the structure and content of the abstract and poster. He wrote and constructed the majority of the abstract and poster, reviewed literature on clinical trials involving cell implantation for Alzheimer's disease, and reflected on potential ethical issues. He also revised and finalised the abstract prior to publication in the journal.

Author 10 (Illes) contributed to the scientific content of the abstract and poster, helped clarify and better elaborate the ideas raised, and critically revised the abstract prior to submission and poster finalization.

Author 1 (Gilbert) contributed to the ethical content of the abstract and poster, helped clarify and better elaborate the ideas raised, and critically revised the abstract prior to submission and the poster prior to printing.

Paper 13, Viaña JNM, Vickers JC, Cook MJ, Gilbert F (2017) Currents of memory: recent progress, translational challenges, and ethical considerations in fornix deep brain stimulation trials for Alzheimer's disease. Neurobiology of Aging 56: 202-210.

Located in Chapter 4

Candidate (Viaña) was the primary and corresponding author, and his contribution comprised 90% of the work for this manuscript. He was mainly responsible for conceptualising the main ideas for this project, organising the structure and flow of the paper, and writing majority of the text. He performed the literature review in scientific, medical, and ethical journals for information presented in this manuscript, especially regarding clinical trials and animal studies of fornix deep brain stimulation. He also filled in the data for, constructed, and formatted the tables. He facilitated the revision of the manuscript, responded to the comments of the editor and reviewers, and carefully proofread it prior to final publication.

Author 13 (Vickers) contributed to the scientific and medical discussion in this paper, helped clarify and elaborate the ideas raised, and critically revised the manuscript prior to submission.

Author 6 (Cook) contributed to the scientific and medical discussion in this paper, helped clarify and elaborate the ideas raised, and critically revised the manuscript prior to submission.

Author 1 (Gilbert) conceptualised the main concept for this paper, contributed to the ethical discussion, helped clarify and better elaborate the ideas raised, and critically revised the manuscript prior to submission.

I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

Signed:

Author 1 (Frederic Gilbert)

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I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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21 June 2018

Author 02 (Susan Dodds)

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Author 3 (Merlin Bittlinger)

I, the undersigned, agree with the above stated "proportion of work undertaken" for each of the above published peer-reviewed manuscripts contributing to this thesis:

Signed:

Author 4 (Roemel Jeusep Bueno)

I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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Author 5 (Adrian Carter)

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I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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Author 6 (Mark Cook)

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Author 7 (Lorena Freitas)

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Author 8 (Eliza Goddard)

I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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Author 9 (Malcolm Horne)

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I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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Author 11 (Cathal D. O'Connell)

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I, the undersigned, agree with the above stated "proportion of work undertaken" for each of the above published peer-reviewed manuscripts contributing to this thesis:

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I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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I, the undersigned, agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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Author 14 (Andrej Vranic)

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I, the undersigned, agree with the above stated "proportion of work undertaken" for each of the above published peer-reviewed manuscripts contributing to this thesis:

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Author 15 (Christian Ineichen)

Appendix 2. Gratis letters and/or permissions to republish in thesis

Publication	**Page**
Gilbert, F, Goddard, E, Viaña, JNM, Carter, A & Horne, M 2017, 'I Miss Being Me: Phenomenological Effects of Deep Brain Stimulation', *American Journal of Bioethics Neuroscience*, vol. 8, no. 2, pp. 96-109.	335
Gilbert, F & Viaña, JN 2018, 'A Personal Narrative on Living and Dealing with Psychiatric Symptoms after DBS Surgery', *Narrative Inquiry in Bioethics*, vol. 8, no. 1, pp. 67-77.	336
Gilbert, F, Viaña, JNM & Ineichen, C 2018, 'Deflating the "DBS causes personality changes" bubble', *Neuroethics*. Article online, published first on June 19, 2018. doi: 10.1007/s12152-018-9373-8.	337
Viaña, JNM, Vickers, JC, Cook, MJ & Gilbert, F 2017, 'Currents of memory: recent progress, translational challenges, and ethical considerations in fornix deep brain stimulation trials for Alzheimer's disease', *Neurobiology of Aging*, vol. 56, pp. 202-210.	340
Viaña, JNM, Bittlinger, M & Gilbert, F 2017, 'Ethical Considerations for Deep Brain Stimulation Trials in Patients with Early-Onset Alzheimer's Disease', *Journal of Alzheimer's Disease*, vol. 58, no. 2, pp. 289-301.	343
Viaña, JNM & Gilbert, F 2018, 'Deep brain stimulation for people with Alzheimer's disease: Anticipating potential effects on the tripartite self', *Dementia*, p. 1471301218761147. Available online first, published on March 11, 2018. doi: 10.1177/1471301218761147.	344

Viaña, JNM, Carter, A & Gilbert, F 2018, 'Of Meatballs and Invasive Neurotechnological Trials: Additional Considerations for Complex Clinical Decisions', *American Journal of Bioethics Neuroscience*, vol. 9, no. 2, pp. 100-104. 346

Viaña, JNM, Illes, J & Gilbert, F 2018, 'Ethical Considerations for Cell Implantation in Alzheimer's Disease - Selected Abstracts From the 2017 International Neuroethics Society Annual Meeting', *American Journal of Bioethics Neuroscience*, vol. 9, no. 1, pp. W9-W10. 346

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Gilbert, F, Viaña, JNM, O'Connell, CD & Dodds, S 2018, 'Enthusiastic portrayal of 3D bioprinting in the media: Ethical side effects', *Bioethics*, vol. 32, no. 2, pp. 94-102. 348

Viaña, JNM & Gilbert, F 2016, 'Big Explanations for Big Expectations: Deriving Lessons from the Human Genome and Blue Brain Projects', *American Journal of Bioethics Neuroscience*, vol. 7, no. 1, pp. 18-20. 347

Gilbert, F, Vranic, A & Viaña, JNM 2016, 'Acquired Pedophilia and Moral Responsibility', *American Journal of Bioethics Neuroscience,* vol. 7, no. 4, pp. 209-211. 347

Viaña, JNM, Freitas, L, Severo, MC & Gilbert, F 2016, 'Decoded Neurofeedback: Eligibility, Applicability, and Reliability Issues for Use in Schizophrenia and Major Depressive Disorder', *American Journal of Bioethics Neuroscience*, vol. 7, no. 2, pp. 127-129. 347

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Pritchard, Laura (ELS-OXF) <L.Pritchard@elsevier.com>

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Cc: Pamela Yeh <pamelalyeh@gmail.com>;

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> Neurobiology of Aging
>
> Dear Ms. Yeh:
>
> Good day! I am a final year PhD student in Neuroethics at the University of Tasmania in Hobart, Australia, and I have published an article in Neurobiology of Aging. I will be submitting my PhD thesis soon, and I would just like to ask if I can incorporate the final published PDF version of this article in my thesis:
>
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>
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> *University of Tasmania*
> *Churchill Avenue, Hobart TAS 7005*
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PhD student in Neuroethics
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Appendix 3. Examiner reports and response to examiners' feedback

Review of “Ethical Considerations for Deep Brain Stimulation and Other Invasive Neurotechnological Trials in People with Alzheimer’s Disease”

Overall, this doctoral dissertation submitted by John Noel M. Viaña for the degree of Doctorate of Philosophy at the University of Tasmania has many merits and strengths such as:

- Very clear writing with clean prose and well-structured papers and dissertation sections;
- An impressive amount of peer-reviewed publications already accepted and published in a short time span;
- Effective engagement in interdisciplinary scholarship;
- Solid contributions to the literature on different fronts, already recognized by peers;
- Extensive and productive scientific collaborations and networking;
- Exquisitely well-researched papers with careful rendition of subtle aspects of clinical trials and of technology.

The main weaknesses are:

- A partially spelled out pragmatic approach (page 19) which, if expanded a bit more upon, would furnish much of the theoretical backbone required for a dissertation. I here invite the author to describe in a page or two the pragmatic approach at the basis of his dissertation. By doing so the candidate would realize how different aspects of the dissertation are held together by this approach but also why there are shortcomings in following this approach which would merit further attention in future work. (It is completely fine to not follow strictly of fully the insights of a given theoretical approach because of practical reasons or other reasons, but it is important to state this explicitly.) I will simply enlist here a few features worth keeping in mind in the progressive deployment of a sophisticated and multifaceted pragmatic approach:
    - The value of understanding the lived experience of those concerned (as stated on page 27, page 86, and pages 175 and 241) but most papers in the dissertation (e.g., page 127, page 136 are good examples), start with a technoscientific point of view and not from the point of view of lived experience and descriptions of problems as encountered by those concerned. For example, one page 41 the all-importance of finding treatments is stated but the pragmatic claimed on page 42 would also require more attention to lived experiences and the needs of patients and families.
    - The importance of context (as described at the top of page 26) as well as the need to adjust ethical responses to changing situations.
    - The importance of empirical research (page 171) in spite of the focus on conceptual research in the thesis (page 179).
    - The desire to produce recommendations and to speak to real-world situations (e.g., page 179, page 180) but more attention to deliberation would be needed in the future given the emphasis placed on deliberation in pragmatism. What is the value of deliberation as a method in opposition to more top-down approaches like principlism which in all fairness is a sort of middle ground between top-down and bottom-up approaches? What is the connection between common principle-based approaches (page 19, page 174) and the pragmatic approach? Pragmatism admits the use of principles but most often considers them as hypotheses to test.

What would this insight mean in the context of the work reported in the dissertation? In terms of eventually testing out the recommendations formulated?

- Fallibilism as stressed in pragmatic theory: What is the author's role (and his collaborators) in generating the PIAAAS bubble (page 108)? If an increasing critical perspective was developed during the process of research and publication (e.g., growing self-awareness), this should be explained to avoid the impression of blaming only others. It would contribute to the epistemological humility and fallibilism promoted by pragmatism. There is also a need to actually enact ethical concepts and theories at some point to assess their value (all of the work published is upstream with little indication of how it will or could be tested.
- The role of empirical research in bioethics scholarship and the constraints on speculation imposed by a pragmatic approach (pages 114 and 115) as well as the interdisciplinary nature of ethics/neuroethics (page 171) but what is the candidate's stance on the role of speculation? Pragmatic approaches stress the value of scenario-based ethical deliberation. Is there a role for speculation (or something akin) therein?
- Working in collaboration with moral agents (few of the papers take the perspective of researchers, their intents, their motivations) such that limited internal understanding of the rationale of researchers is reflected. Resolving ethical problems is facilitated by the understanding of the motivations of people as agents. However, researcher voices are quite absent from the thesis and the development of recommendations (page 171). There is no engagement process supporting the development of recommendations.

- The concerns about the risks of genetic information (pages 136-148) could be lessened if the patient is already diagnosed with AD?
- The use of the concept of "transdisciplinary research" (page 18), "transdisciplinary approach" (page 19), "transdisciplinary pragmatic approach" (page 26), transdisciplinary analysis (page 179), transdisciplinary nature of neuroethics (page 205) and so on... merits elucidation, notably where many hesitate to claim such a high level of integration for neuroethics. Most authors describe neuroethics as an interdisciplinary field and nevertheless there are some who still challenge this view. I am not sure the candidate can claim the thesis to be an exemplar of transdisciplinary research. It would be advisable to redescribe the work. Also, the explanation of the transdisciplinary nature of neuroethics as being premised on the interdisciplinary nature of neuroscience (pages 170-171) is not the most convincing. Yes, in a sense the complexity of neuroscience as a field merits a complex response but are there not stronger arguments justifying the interdisciplinary nature of neuroethics (from a pragmatic perspective)?
- Some tensions between the criticisms about speculation in and the actual engagement in scholarship which seems to rely itself on an economy of promises because it is not grounded in actual lived experience of stakeholders. Indeed, many if not all of the contributions are premised on a rather narrow description of the problem addressed, often starting with technological development and clinical research with little integration of social context and relational aspects of situations experienced by patients and their relatives. In the future, adopting a pragmatic approach should infuse theoretical and methodological orientations such that situations are not solely defined by their techno-scientific dimensions but also their personal, interpersonal aspects dimensions too. Page 119: Why is speculative ethics wrong? You should spell out what is your own ideal of ethics scholarship, otherwise you fall into crypto-normativism: you suggest implicitly a normative vision without spelling it out yourself.

Throughout the thesis, there is no contextual analysis for the reasons/causes of speculation in ethics scholarship.

- There is no general imitations section, no acknowledgment of what was fulfilled and not fulfilled by the doctoral research project

Minor comments (typos, formulations)

- Missing "on-going" in "on practices and research involving" (page 18)?
- "has written" and not "has wrote" (page 24)
- "these papers are" and not "these papers will" (page 24)
- "this chapter includes" and not "this chapter will include articles" (page 24)
- "also illustrates" instead of "will also illustrate" (page 25)
- Nuance the lack of advocacy for PET scan for diagnostic purposes given its (potentially hasty) admission in the USA (to differentiate between different forms of dementia? (page 33)
- Missing "not" in "was able to" on page 46
- Change "would be useful" for "will be useful" (page 51)
- Insert "the" in "for the informed consent procedure and the design of DBS..." (page 51)
- Why is the therapeutic use of electric stimulation not dated back to the Ancient civilizations (page 52) and actually to 1936-7
- Does "leisure tourism" (page 61) stand for sex tourism? If that's the case it should be spelled out very transparently without any euphemism
- "to cross an international boarder" instead of "cross the border" (page 65)
- Check syntax in "various qualitatively different kinds..." (page 66)
- I wondered if the repeated statements "are included in this manuscript" (e.g., page 69, page 107, page 214 and so on) should not be changed to something like "are included in this thesis" or "are included in this doctoral dissertation"
- page 77, not clear what the "#" stands for in the table
- Typo in "[7]., etc." (page 109)
- How do know that the "prevalence of evidence" was not biased by conflicts of interest" (page 117). Why are you so confident in the prevalence rates reported? (page 117)
- Why "Nonetheless" in "Nonetheless, this study"? A pragmatic model of philosophy does not antagonize conceptual and empirical research (page 171).
- Change "more closely on peculiarities" to "more closely at peculiarities" (page 177)
- Change "Throughout the PhD" for "Throughout my doctoral research" (page 205)
- Insert "project" after "A possible bioethical research" (page 209)
- Provide a reference for the "applied and pragmatic ethical approach" (page 242)
- Confusion between practical and pragmatic (page 242 and 244)

I encourage the candidate to continue his work, enrich his understanding of pragmatism and pursue a research program where layers of meaning and of methodologies will be explored. This doctoral dissertation is a highly promising start to independent research.

November 30 2018

Dear Chair of Examiners,

Re: Examiner Report, John Noel M. Viaña Thesis

Thank you for the opportunity to review John Noel M. Viaña's Thesis entitled "*Ethical Considerations for Deep Brain Stimulation and Other Invasive Neurotechnological Trials in People with Alzheimer's Disease*". My recommendation is that the degree be awarded provided minor revisions and textual changes identified in external examiners' reports are undertaken to the satisfaction of the Chair of Examiners.

The thesis explores ethical issues in the use of deep brain stimulation for persons with Alzheimer disease using an interdisciplinary approach. The candidate reviews relevant animal studies and clinical trials and lists ethical concerns related to genetic,

neurobiological, cognitive and societal dimensions of the application of deep brain stimulation for Alzheimer disease. The candidate integrates his findings into sets of recommendations for future clinical trials, including around considerations such as patient selection, study design, and return of results.

Overall, this thesis is a pleasure to read. The writing is clear, and the content is well organized. **Strengths of the manuscript include**:

- The body of work presented examines ethical considerations across the spectrum of clinical research, from animal studies to clinical trials in humans. This is especially relevant as deep brain stimulation remains relatively new (in its current format) and will likely continue to be investigated in animal models for many years.
- The background description of Alzheimer disease is interwoven with brief comments on the topic of ethical implications, which ties together the overall topic of the thesis and highlights the in-depth expertise of the candidate.
- The main manuscripts each provide sets of key pragmatic recommendations in moving forward with deep brain stimulation for Alzheimer disease, for example on the topics of for patient selection and trial design. In my opinion these constitute the main strength of the thesis and ensure the work has real world relevance and application.
- The discussion section extends the candidate's body of work to other technologies and covers a wide range of associated ethical and social issues such as media representations, which demonstrates an impressive breadth of knowledge.

The thesis would benefit from addressing a few **key areas for improvement:**

- It would be useful to include a brief section, or even simply a paragraph, that consists in a narrative about the methodology employed, in particular for the first two main publications. The justification for the choice of methodology (for example, versus a scoping or systematic review) as well as additional details about how and

which publications were selected as part of the review would be critical to provide context for the body of work.

- Within the section about methodology, I would invite the candidate to provide an in-depth description of how the analytical framework was applied and how the recommendations were formed. As one example, for the recommendations about verifying if fornix stimulation triggers autobiographical memory as a marker of eventual therapeutic response – what methodology was employed to derive these recommendations from the literature? Which metrics were used to determine if an occurrence described in the literature warranted a recommendation?
- During his thesis defense, I would recommend that the candidate explore how the same research questions could be addressed using a hypothesis-based approach.

Minor comments about the manuscript include:

- The thesis would benefit from figures, in particular one on the potential mechanisms of action of deep brain stimulation and one on the clinical features of Alzheimer disease progression, to aid in setting the context.
- Studies of identity and selfhood in deep brain stimulation are often qualitative in nature as dictated by the research question, which can limit their representativeness as the candidate aptly points out in a statement on page 105. The candidate may wish to comment on the various biases researchers may encounter when conducting qualitative work (e.g., interview studies).
- The candidate should revise the introduction and discussion sections and eliminate the use of imprecise language (e.g., “has taken off”, page 18).
- In the current state of uncertainty in the quality of peer-reviewed journals, the candidate may want to define Q1 journals (page 20).
- As some individuals with Mild Cognitive Impairment (MCI) do not convert to Alzheimer disease, I would suggest avoiding likening MCI to “pre-dementia” (page 32).
- In the introduction chapters, I would suggest moving the pathophysiology section ahead of the other topics, as there are discussions of A-beta and tau embedded into

other sections (e.g., genetics) and it may be helpful for the flow of the thesis to describe and define these hallmarks first.

- I would encourage the candidate to reference the sentence that describes the benefits of Alzheimer disease drugs (page 41) as these are somewhat debated in the dementia research community.

In summary, I found this thesis well-written and interesting, with the key strength of putting forward novel recommendations with real world relevance. I commend the candidate for the depth and breadth of his work and the impressive volume of his body of work, both as lead author and as co-author. I wish him the very best in his future career endeavours.

January 29, 2019

Dirk Baltzly, Ph.D.
Chair of Examiners
Philosophy and Gender Studies Program
School of Humanities
College of Arts, Law, and Education
University of Tasmania

Re: Response to the examiners' comments on the PhD thesis entitled "Ethical Considerations for Deep Brain Stimulation and Other Invasive Neurotechnological Trials in People with Alzheimer's Disease"

Dear Prof. Baltzly:

Good day! Thank you very much for considering my PhD thesis on "Ethical Considerations for Deep Brain Stimulation and Other Invasive Neurotechnological Trials in People with Alzheimer's Disease" and for providing me with the opportunity to revise it. I greatly appreciate the time, attention, and effort that the two examiners took to review my PhD thesis and suggest points for improvement. I would also like to thank both examiners for pointing out the merits and strengths of my doctoral dissertation, recommending that my degree be awarded after minor revisions, and suggesting some textual changes. I have carefully reviewed the feedback provided by each examiner and have revised my dissertation accordingly. In general, I have expanded my discussion on pragmatic ethics and on the limitations of this dissertation, as suggested by Examiner 1, and I have also elaborated on the method I employed to come up with the recommendations made in the three main publications in this thesis, as suggested by Examiner 2. Kindly find below a tabulation of the suggestions made by each examiner and my responses to these comments, highlighting the textual changes I have made in the manuscript to account for the feedback provided.

Responses to Examiner 1's comments and recommendations

Main weaknesses	
Suggestion/Feedback	**Response**
A partially spelled out pragmatic approach (page 19) which, if expanded a bit more upon, would furnish much of the theoretical backbone required for a dissertation. I here invite the author to describe in a page or two the pragmatic approach at the basis of his dissertation. By doing so the candidate would realize how different aspects of the dissertation are held together by this approach but also why there are shortcomings in following this approach which would merit further attention in future work. (It is completely fine to not follow strictly of fully the insights of a given	I would like to thank Examiner 1 for inviting me to spell out the pragmatic approach at the basis of my dissertation. I have added the following paragraphs, which can be found on pages 3 to 7 of Chapter 1, to describe the pragmatic approach I used: "In addition to taking an interdisciplinary lens, this thesis also utilises an empirical, applied, and pragmatic bioethical approach (Fins, Miller & Bacchetta 1997, 1998; Racine 2008a, 2008b). Pragmatism, a philosophical tradition that originated from the USA around 1870 and initially forwarded by Charles Sanders Peirce, William James, and John Dewey, emphasises the clarification of the contents of hypotheses by tracing their practical consequences or implications for what we will or should do (Hookway 2013). The version of pragmatism in

theoretical approach because of practical reasons or other reasons, but it is important to state this explicitly.)	bioethics that is applied in this work draws upon from the moderate natural pragmatism forwarded by Eric Racine (2008b, 2013) and the clinical pragmatism method proposed by Joseph Fins, Matthew D. Bacchetta, and Franklin G. Miller (1997, 1998), both of which were mainly or partly inspired by John Dewey's formulation of pragmatism, which emphasises that moral problem solving should be based on the experimental method of inquiry (Fins, Bacchetta & Miller 1997). Dewey's naturalistic metaethics of value judgements, grounded in developmental and social psychology, argues the use of reflective intelligence in revising our judgements in light of the consequences brought about by acting on them, allowing redirection of conduct when habits fail. Through an experimental method of inquiry, value judgements are tested by putting them into practice and assessing whether the results are satisfactory in the way they solve problems while limiting side effects to an acceptable level, enable successful outcomes to new problems, and provide satisfactory results when compared to alternative value judgements. Dewey's ethics distinguishes itself by focusing on human conduct as warrant for value judgements, rather than on a fixed reference point such as Platonic Forms, God's command, nature, or pure reason (Anderson 2018). Racine's (2013) reading of Dewey's (1922) pragmatism highlights his view of pragmatism as an approach that stresses how ethical behaviour and thinking are contextual. Racine compares it with Beauchamp's and Childress's principlism (2009), and emphasises how pragmatism reflects more on aspects of social justice, empirical research's transformative role, and institutional and macro-level changes on health policy due to the influence of democracy and deliberation in the construction of shared common goods (Racine 2013). Furthermore, his perspective on pragmatism emphasises the positive contribution of science to debates on ethics and policy but also challenges various forms of foundationalism in philosophy and science. In addition to Dewey's (1922) pragmatism, Racine (2008b) has also drawn upon the work of various philosophers such as Van Rensselaer Potter on bioethics being the bridge between science and the humanities; Anne Fagot-Largeault on the auto-regulation process that is based on social adaptation in bioethics; and Jonathan Moreno on pragmatism's rejection of fundamental ethical principles that rely on *a priory* inquiry. By using ideas from various pragmatists, Racine (2008b) then proposes that a

	moderate pragmatic naturalism best describes the state bioethics has taken in order to respond to new healthcare situations and scientific advances. The theoretical commitments of Racine's (2008b) moderate pragmatic naturalism are: "1) Distinction between 'is' and 'ought' granted with qualifications; 2) Ethical predicates are properties that cannot be reduced to natural properties but are best understood within a fact-value continuum; 3) Empirical knowledge does not bring ethical justification of ethical norms but ethical knowledge must take into account human capacities. 'Is' does not imply 'ought' but 'ought' implies 'can'; 4) Ethical norms are not natural laws but norms and rules proper to human social life. There are no natural moral laws but moral rules can be better understood from a factual point of view that takes into consideration constraints to moral agency; 5) Ethical norms do not simply follow from reason or experience but from their interaction, e.g. reflexive equilibrium; 6) Bioethics is neither autonomous nor heteronomous but best described as an interdisciplinary field with practical goals such as creating new forms of wisdom in the delivery of healthcare and the pursuit of health; 7) Normative ethics is normative. Metaethics is both empirical and conceptual." (p. 98, Racine 2008b) Racine (2008b) forwards that moderate natural pragmatism "expresses some of the commitments required for the flourishing of new forms of wisdom for the delivery of healthcare and the pursuit of health" (p. 100, Racine 2008b). Through the lens of pragmatist bioethics, Racine has advocated for the acknowledgement of pluralism in neuroethics and for more active involvement of physicians, allied healthcare personnel, and stakeholders in improving healthcare (Racine 2008a). He has also used this framework to investigate the effect of media depictions of disorders of consciousness on public perceptions on disorder prognosis; the differing opinions of physicians, and the contextual and personal factors influencing such, on the prognosis of people with disorders of consciousness (Racine 2008b); and the reason for ongoing controversies on death determination and why lay and foundational expert views need to co-evolve in order to reconstruct the meaning of death considering its practical importance (Racine 2015).

	Another perspective greatly inspired by Dewey's (1922) pragmatism is that of Fins, Bacchetta, and Miller (1997, 1998), who proposed clinical pragmatism as a method of problem solving. The goal of clinical pragmatism is to reach consensus on good outcomes in real clinical cases posing moral problems. This is achieved by a thorough process of inquiry, discussion, negotiation, and reflective evaluation, treating moral rules and principles as hypothetical guides for conduct rather than as fixed and absolute moral laws (Fins, Bacchetta & Miller 1997). In clinical pragmatism, health practitioners engage in a collaborative process of problem solving when they "(1) assess the patient's medical condition; (2) determine and clarify the clinical diagnosis; (3) assess the patient's decision-making capacity, beliefs, values, preferences, and needs; (4) consider family dynamics and the impact of care on family members and others intimately concerned with the patient's well-being; (5) consider institutional arrangements and broader social norms that may influence patient care; (6) identify the range of moral considerations relevant to the case in a manner analogous to the clinical process of differential diagnosis; (7) suggest provisional goals of care and offer a plan of action including plausible treatment and care options; (8) negotiate an ethically acceptable plan of action; (9) implement the agreed upon plan; (10) evaluate the results of the intervention; and (11) undertake periodic review and modify the course of action as the case evolves" (p. 131, Fins, Bacchetta & Miller 1997) Ultimately, clinical pragmatism focuses on the interpersonal process of moral problem solving, and as such, it requires being able to take others' perspectives, engage in deliberative dialogue, and negotiate questions of meaning and the goals of care to reach an informed and inclusive consensus (Fins, Bacchetta & Miller 1997, 1998). Using the case of a person with Parkinson's disease who became non-arousable due to a yeast infection, has poor prognosis, and who has a wife who wanted him to receive all aggressive measures including cardiopulmonary resuscitation, Fins, Bacchetta, and Miller (1997) illustrated how clinical pragmatism can be used by the physician to undertake authentic communication with the wife and achieve consensual decision on the appropriate therapeutic course at the end of life, taking into account situational, relational, institutional, social, religious, and cultural factors influencing decision making (Fins, Bacchetta & Miller 1997). Clinical pragmatism has also been used by Fins

	(2005) to identify challenges in the care of patients with severe brain injury and on ways in which a proper plan of palliative care can be negotiated with surrogates, considering medical facts and the values of the patient and surrogates while ensuring balance between burdens and benefits." In the first half of the paragraph on page 9 of Chapter 1, I have also described challenges and possible shortcomings of pragmatism. "It is important to acknowledge that the experimental method championed by pragmatism also has its challenges, particularly in determining whether the tested principles provide the necessary guidance to a situation and lead to desired consequences. Although, consensus can be viewed as a potential way of determining the success of a tested principle, the influence of inequalities in power, wealth, and information should not be disregarded (Arras 2002) as this could easily degenerate pragmatism into clinical manipulation and become a way for the physician to reassert paternalism (Tong 1997). Nonetheless, considering pragmatism's (Fins, Bacchetta & Miller 1997; Racine 2008b) dynamism, self-reflexivity, and fluidity and its commitment to modest fallibilism (Arras 2002), this approach provides adequate opportunity for self-correction (Brown 2008) should initial consensus prove to exacerbate rather than ameliorate paternalistic attitudes and undermine patient autonomy. Furthermore, even though consensus cannot be achieved, an open and honest discussion and deliberation could still result to the goods of mutual respect and trust between participants and health professionals (Tong 1997)."
The value of understanding the lived experience of those concerned (as stated on page 27, page 86, and pages 175 and 241) but most papers in the dissertation (e.g., page 127, page 136 are good examples), start with a technoscientific point of view and not from the point of view of lived experience and descriptions of problems as encountered by those concerned. For example, one page 41 the all-importance of finding treatments is stated but the pragmatic claimed on page 42 would also require more attention to	I greatly appreciate Examiner 1's suggestion of giving more attention to the lived experiences and needs of families and patients in the pragmatic claimed on page 36. I have already expanded the section on interventions for people with Alzheimer's disease, adding this paragraph on pages 36 to 37 of Chapter 2: "Although the focus of this thesis is on invasive treatment modalities that primarily aim to improve the cognition of people with AD, it is important not to discount the importance of social and environmental interventions that provide additional support and help improve the quality of life and well-being of people with AD and their caregivers (Quinn et al. 2016; Vandepitte et al. 2016; Whitlatch & Orsulic-Jeras 2018). In

lived experiences and the needs of patients and families.	addition, evaluating the value of interventions, regardless of their nature and invasiveness, should always take into account effects that extend beyond the biology of the person with AD, acknowledging how they could also influence daily function and living, relationality, and sociocultural integration. “
The importance of context (as described at the top of page 26) as well as the need to adjust ethical responses to changing situations.	I would like to thank Examiner 1 for recommending further emphasis in this dissertation on the importance of context and the need to adjust ethical responses to changing situations. I have added the phrase “in medical details and social context” in this sentence on page 19 of Chapter 1 to underscore this point: “Although this thesis acknowledges the usefulness of existing ethical publications (Pierce 2014; Ovadia & Bottini 2015; Siegel, Barrett & Bhati 2017; Bittlinger & Müller 2018) and even recommends extending the ethical frameworks and ideas raised in them to other technologies for dementia, it also aims to underscore the importance of accounting for nuances in medical details and social context, and adapting, reconciling, and/or reframing ethical discussions and recommendations to accommodate these specificities and differences, as in the case of DBS for people with early-onset AD.”
The importance of empirical research (page 171) in spite of the focus on conceptual research in the thesis (page 179).	I appreciate Examiner 1’s suggestion that the importance of empirical research on the ethics of DBS for AD be elaborated further, in spite of the focus of this thesis on conceptual research. I have added or expanded the following sentences in Chapter 7 to account for this feedback: Page 173: “Pragmatically-oriented (Fins, Bacchetta & Miller 1997; Racine 2008b) conceptual work on this topic could serve as the basis of future actual empirical work involving deliberation and engagement with various key stakeholders, allowing better understanding of the perspectives of people with AD on participating in a risky and invasive clinical trial and the intentions and motivations of researchers in extending the application of DBS to AD.” Page 183: “In order to adopt a full pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b), recommendations in the three main publications should be tested and deliberated upon in future empirical bioethical studies involving people with AD

	who have received or will receive DBS, and on future conceptual and empirical neuroethical research on new findings from the clinical trials examined (Leoutsakos et al. 2018), or on DBS of other brain regions (Scharre et al. 2018) or DBS with a closed-loop set-up (Senova, Chaillet & Lozano 2018) in people with AD."
The desire to produce recommendations and to speak to real-world situations (e.g., page 179, page 180) but more attention to deliberation would be needed in the future given the emphasis placed on deliberation in pragmatism. What is the value of deliberation as a method in opposition to more top-down approaches like principlism which in all fairness is a sort of middle ground between top-down and bottom-up approaches? What is the connection between common principle-based approaches (page 19, page 174) and the pragmatic approach? Pragmatism admits the use of principles but most often considers them as hypotheses to test. What would this insight mean in the context of the work reported in the dissertation? In terms of eventually testing out the recommendations formulated?	I greatly appreciate Examiner 1's recommendation of including a more detailed discussion on the importance of deliberation in pragmatism and its relation and comparison to principlism, particularly in the context of this body of work. I have added or expanded the following statements to address these suggestions: Chapter 1, pages 7 to 8: "Although pragmatism in bioethics focuses more on a deliberative and dynamic approach to decision-making rather than on the direct top-down application of bioethical principles and moral laws (Fins, Bacchetta & Miller 1997; Racine 2008b), certain moral rules, principles, and guidelines can still be used as hypotheses or as available frameworks for analysing moral situations (Arras 2002) and determining the most appropriate ethical course of action in a particular context. In this thesis, principles from various guidelines such as the Nuremberg Code, Declaration of Helsinki, Belmont Report, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects are used to evaluate clinical trials on their social or scientific value, scientific validity, subject selection, risk-benefit ratio, study design, informed consent procedure, communication of research results, and treatment of participants (Emanuel, Wendler & Grady 2000; Li et al. 2016). Although not explicitly stated all the time, the ethical considerations forwarded throughout this dissertation are also guided by the four key principles in medical ethics, which are respect for autonomy, beneficence, non-maleficence, and justice (Beauchamp & Childress 2013). The application of a pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) means that no principle takes precedence or priority over the others; rather, these principles are just used as guides to determine the most appropriate course of action to protect and promote the welfare of research participants and other stakeholders, taking into account scientific and medical knowledge, relational and social dimensions of living with AD and/or receiving an invasive intervention such as DBS, and the context in which the trial is performed and where decisions are

	made. By utilising a pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) guided by cornerstone ethical guidelines and medical ethics principles to evaluate different aspects of a clinical trial (Emanuel, Wendler & Grady 2000; Li et al. 2016), this dissertation and the publications in it emulate the clinical and research ethics-grounded analysis performed by Issa and Keyserlingk (2000), Karlawish and Casarett (2001), Karlawish and Clark (2002), Beattie (2007), and Fisk (2007) to dissect ethical issues in research involving people with dementia and by Cabrera, Evans, and Hamilton (2014), Clausen (2010), and Racine, Bell, and Zizzo (2014) to determine ethical considerations on the expanding use of DBS." Chapter 7, page 177: "The "Participant selection criteria" section in Chapter 4 (Viaña et al. 2017) and the "Considerations for patient selection" section in Chapter 5 (Viaña, Bittlinger & Gilbert 2017) both discuss ways in which the selection criteria can be improved to ensure that participants are not subjected to undue and avoidable harms and also potentially benefit from the procedure, in line with the ethical principles of beneficence and non-maleficence (Beauchamp & Childress 2013) and with pragmatism's (Fins, Bacchetta & Miller 1997; Fins 2008b) goal of providing practical goals and realizable plans of action." Chapter 7, page 183: "In order to adopt a full pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b), recommendations in the three main publications should be tested and deliberated upon in future empirical bioethical studies involving people with AD who have received or will receive DBS, and on future conceptual and empirical neuroethical research on new findings from the clinical trials examined (Leoutsakos et al. 2018), or on DBS of other brain regions (Scharre et al. 2018) or DBS with a closed-loop set-up (Senova, Chaillet & Lozano 2018) in people with AD."
Fallibilism as stressed in pragmatic theory: What is the author's role (and his collaborators) in generating the PIAAAS bubble (page 108)? If an increasing critical perspective was developed during the process of research and publication (e.g., growing self-awareness), this should be explained to avoid the impression of	I would like to thank Examiner 1 for asking further clarification on the role of the author and his collaborators in generating the PIAAAS (personality, identity, agency, authenticity, autonomy, and self) bubble and for emphasizing the need to actually enact ethical concepts and theories at some point to assess their value. I have added following paragraph on pages 104 to 106 of Chapter 3 to respond to and integrate this feedback in my dissertation:

blaming only others. It would contribute to the epistemological humility and fallibilism promoted by pragmatism. There is also a need to actually enact ethical concepts and theories at some point to assess their value (all of the work published is upstream with little indication of how it will or could be tested.	"Our article on the potential ethics bubble on the effects of DBS on PIAAAS (Gilbert, Viaña & Ineichen 2018) has encouraged deeper reflection on how my and my collaborators' previous conceptual and empirical works could have likewise contributed to an ethics bubble, and on how future work conducting empirical research or drawing from results of qualitative studies could be improved so as not to create an impenetrable bubble that distorts accurate perception of actual risks and potential benefits of a certain technology or intervention. One evidence of such reflection is the citation of Frederic Gilbert's (2013, 2015) previous works on how DBS in people with treatment-resistant depression could lead to self-estrangement. In the article of Gilbert, Viaña and Ineichen (2018), the papers of Gilbert (2013, 2015) were included in Table 2 as examples of philosophical explanations about the putative impact of DBS on PIAAAS. Including Gilbert's (2013, 2015) papers as possible contributors to the PIAAAS bubble is evidence of growing self-awareness and an increase in critical perspective during research and publication, in line with pragmatism's (Fins, Bacchetta & Miller 1997) emphasis on periodic review and in modifying previously proposed courses of action as research evolves. The critical appraisal of one's previous work is also a demonstration of commitment to moderate fallibilism and epistemological humility advocated by pragmatism (Arras 2002), acknowledging how one's previous views could have contributed to an ethics bubble and how this could be corrected. The use of the term "we neuroethicists" or "we, the neuroethicists" in the paper also exemplifies that the goal of the article of Gilbert, Viaña and Ineichen (2018) is not to simply delegate blame to other ethicists for generating hype on the extended effects of DBS, but also to critically appraise one's previous work and the way it has also contributed to the generation of a speculative bubble. Finally, in order to achieve a full pragmatic approach (Fins, Bacchetta & Miler 1997; Racine 2008b) in addressing the issue of ethics hype on the effects of DBS on PIAAAS, it is important to facilitate deliberation with patients, physicians, and ethicists on how they perceive philosophical reflections on DBS's effects on PIAAAS could affect patient willingness to undergo DBS and physician decision to offer it as a potential therapy. This deliberation would allow testing of the practical usefulness and applicability of the recommendations forwarded by Gilbert, Viaña, and Ineichen (2018) and also espouse mutual trust and respect among various stakeholders (Tong 1997) in the applications of

	DBS to movement disorders and in its expanding therapeutic applications."
The role of empirical research in bioethics scholarship and the constraints on speculation imposed by a pragmatic approach (pages 114 and 115) as well as the interdisciplinary nature of ethics/neuroethics (page 171) but what is the candidate's stance on the role of speculation? Pragmatic approaches stress the value of scenario-based ethical deliberation. Is there a role for speculation (or something akin) therein?	I am grateful for Examiner 1's questions on my stance on speculation and on whether I believe that there is role for speculation in a pragmatic ethical approach. I have added the following paragraph on pages 106 to 108 of Chapter 3 to address the examiner's queries: "Although Gilbert, Viaña, and Ineichen (2018) caution against unwarranted and unsubstantiated speculation on the effects of DBS on PIAAAS, we do not aim to disregard the role and importance of speculation. Speculation in bioethics involves an attempt to predict scenarios and draw conclusions on their possible outcomes based on assumptions that cannot be verified by present empirical or scientific claims. We acknowledge that through this effort, major ethical challenges can be foreseen before a novel technology or a new application of an existing technology is introduced and disseminated (Racine et al. 2014), allowing adequate steps to be taken to avert or deal with these challenges (Roache 2008). Furthermore, we agree with Roache (2008) that properly grounded and knowledge-based speculation (Racine et al. 2014) encourages ethical evaluation at the start or early stages of a project, helping avoid unethical or ethically misguided scientific endeavours before a significant amount of money, time, and careers has been invested in them. Speculation, even of future scenarios with low probabilities of occurring, could also be instrumental in motivating the conduct of crucial ethical projects (Roache 2008) that address present issues. Pragmatism's commitment to fallibilism (Arras 2002), acknowledging that knowledge is not absolute (Brown 2008), also signifies room for making speculations, as long as they follow a thorough review of empirical information (Fins, Bacchetta & Miller 1997; Fins 2005) and discuss the limitations of various methods in obtaining such information, as indicated in the paper of Gilbert, Viaña, and Ineichen (2018) and in one of the preceding paragraphs. With pragmatism's emphasis on scenario and context-based ethical deliberation (Fins, Bacchetta & Miler 1997; Racine 2008b), it is important to critically appraise previous speculations and conclusions made to see how well they still fit within a particular context and the extent of the applicability of any claims made. For instance, the article of Gilbert, Viaña, and Ineichen (2018) highlighted that "the prevalence and incidence of effects on PIAAAS might not

	be exclusively correlated with a specific DBS target and/or stimulation parameter. It should rather be seen as a result of the interaction between electrical stimulation, adjustments in medication, and natural progression of the disease" (p. 10, Gilbert, Viaña & Ineichen 2018). This claim underscores the significance of context in translating ethical claims. In addition to taking into account biological details of a case, it is essential to factor in family dynamics, institutional arrangements, social norms (Fins, Bacchetta & Miller 1997), cultural practices, and broader environmental factors that could affect the extent in which a person receiving DBS adjusts and adapts to DBS therapy. The applicability, importance, and relevance of any speculations made should be viewed from both techno-scientific and psycho-socio-environmental vantage points, considering not just the perspectives of people receiving DBS but also of the attending medical professionals and of family and caregivers. Finally, fallibilism should be applied to both qualitative and quantitative claims. Potential biases due to conflicts of interest (Bebbington 2003) and/or limitations and challenges in gathering comprehensive quantitative information (Fairchild et al. 2018) should be acknowledged when presenting and drawing claims from quantitative data. For instance, the applicability to ethical claims of prevalence rates of various psychiatric symptoms in people with Parkinson's disease indicated in the paper of Gilbert, Viaña, and Ineichen (2018) might be affected by location, time period, specific patient population, institutional capacities, and other socio-environmental factors that influence the reporting and diagnosis of psychiatric symptoms (Woodall et al. 2010; Kohrt et al. 2014)."
Working in collaboration with moral agents (few of the papers take the perspective of researchers, their intents, their motivations) such that limited internal understanding of the rationale of researchers is reflected. Resolving ethical problems is facilitated by the understanding of the motivations of people as agents. However, researcher voices are quite absent from the thesis and the development of recommendations (page 171). There is no engagement process supporting the development of recommendations.	I would like to thank Examiner 1 for pointing out that researcher voices are quite absent from this thesis and in the development of recommendations and that there is no engagement process in the development of recommendations. I have added the following statements in this thesis to acknowledge these points and underscore the importance of involving researchers, clinicians, and other allied healthcare personnel in future ethical investigations on clinical trials of deep brain stimulation for Alzheimer's disease: Chapter 1, pages 12 to 13: "At this point, it is also important to stress what this dissertation does not try to achieve. First, although pragmatic ethics focuses on the role of deliberation and negotiation (Fins,

	Bacchetta & Miller 1997; Racine 2008b), research for this dissertation does not include direct engagement with people participating in DBS for AD clinical trials, their family members and/or caregivers, and researchers and clinicians having an active role in the conduct of these trials, given that none of the trials are performed in Australia. As such, this dissertation employs a relatively limited pragmatic approach." Chapter 7, page 173: "Pragmatically-oriented (Fins, Bacchetta & Miller 1997; Racine 2008b) conceptual work on this topic could serve as the basis of future actual empirical work involving deliberation and engagement with various key stakeholders, allowing better understanding of the perspectives of people with AD on participating in a risky and invasive clinical trial and the intentions and motivations of researchers in extending the application of DBS to AD." Chapter 8, pages 247 to 248: "Interviews and surveys with researchers, scientists, doctors, and other medical professionals who are conducting DBS for AD trials and/or are involved in laboratory research relevant to this topic should also be performed. This will be crucial in acquiring a fuller understanding of the state of knowledge and research in this field; preliminary evidence on the potential safety and efficacy of DBS for AD beyond what is available in academic publications; motivations for pursuing this line of work in a vulnerable population, despite limited evidence; factors and considerations undertaken in participant recruitment, trial design, and selection of outcome measures; and personal reflection on possible ethical issues arising from the conduct of these clinical trials. To incorporate negotiation and deliberation (Fins, Bacchetta & Miller 1997; Racine 2008b), focus groups involving various stakeholders can be facilitated, allowing joint discussion on ethical issues from multiple perspectives and collaborative decision-making on possible ways in which they can be addressed. In these studies, a hypothesis-based approach could also be employed to determine how certain factors such as decision-making capacity of people with AD and their family members and possible conflicts of interest of researchers could influence their perceptions of ethical dilemmas and moral concerns arising from DBS for AD trials."

The concerns about the risks of genetic information (pages 136-148) could be lessened if the patient is already diagnosed with AD?	I would like to thank Examiner 1 for asking whether the risks of genetic information could be lessened if a person with AD has already received clinical diagnosis. I have added a few sentences on page 179 of Chapter 7 to address this query: "Although concerns on the risks of genetic information to an individual with AD could be lessened if there is already a clear diagnosis of AD, some other risks to that person and to his or her family members remain. For instance, information on having autosomal-dominant mutations linked to early-onset AD could lead to prognostic pessimism (Kong, Dunn & Parker 2017) on some individuals regarding their rate of decline and possible eventual appearance of behavioural (Cacace, Sleegers & Van Broeckhoven 2016) and motor symptoms (Wu et al. 2012) associated with autosomal dominant AD, especially in the absence of proper post-test genetic counselling (Viaña, Bueno & Gilbert 2017). Genetic information could also have repercussions on family members, primarily on children and immediate relatives. A positive genetic test result for possession of autosomal dominant AD associated alleles means that children and siblings could also have the mutation, which would have implications on insurance (Roberts, Christensen & Green 2011), reproductive (Goldman 2012), and geriatric care planning, in addition to decisions on participating in a clinical trial for those with autosomal dominant AD (Van Cauwenberghe, Van Broeckhoven & Sleegers 2015) and getting a genetic test themselves."
The use of the concept of "transdisciplinary research" (page 18), "transdisciplinary approach" (page 19), "transdisciplinary pragmatic approach" (page 26), transdisciplinary analysis (page 179), transdisciplinary nature of neuroethics (page 205) and so on... merits elucidation, notably where many hesitate to claim such a high level of integration for neuroethics. Most authors describe neuroethics as an interdisciplinary field and nevertheless there are some who still challenge this view. I am not sure the candidate can claim the thesis to be an exemplar of transdisciplinary research. It would be advisable to redescribe the work. Also, the explanation of the transdisciplinary nature of neuroethics as being premised on the	Upon careful reflection, I agree with Examiner 1 that the level of integration in neuroethics is mostly at the interdisciplinary, rather than at the transdisciplinary, level. The application and synthesis of multiple disciplinary vantage points have allowed the proposition of practical recommendations, but indeed, not the creation of a totally novel field and methodology that transcend individual disciplinary perspectives (Choi & Pak 2006). Contributions from distinct disciplines can still be identified and pointed out in neuroethical discourses. As such, I have already redescribed this concept in this work and have change all mentions of "transdisciplinary" to "interdisciplinary", including variations of these terms. To address Examiner 1's request for a stronger argument on the interdisciplinary nature of neuroethics (from a pragmatic perspective), I have extended the following statement on pages 172 to 173 of Chapter 7:

interdisciplinary nature of neuroscience (pages 170-171) is not the most convincing. Yes, in a sense the complexity of neuroscience as a field merits a complex response but are there not stronger arguments justifying the interdisciplinary nature of neuroethics (from a pragmatic perspective)?	"Given the interdisciplinary nature of neuroscience, it is just befitting for a field that investigates and explores the ethical dimensions of this discipline to acknowledge the benefits of looking at different levels of biopsychosocial organization and through different disciplinary lenses. Furthermore, from a pragmatic standpoint (Fins, Bacchetta & Miller 1997; Racine 2008b), understanding the ethical and societal implications of neuroscientific development necessitates the use of empirical knowledge and methods from both the natural and social sciences, taking into account scientific facts and social norms."
Some tensions between the criticisms about speculation in and the actual engagement in scholarship which seems to rely itself on an economy of promises because it is not grounded in actual lived experience of stakeholders. Indeed, many if not all of the contributions are premised on a rather narrow description of the problem addressed, often starting with technological development and clinical research with little integration of social context and relational aspects of situations experienced by patients and their relatives. In the future, adopting a pragmatic approach should infuse theoretical and methodological orientations such that situations are not solely defined by their techno-scientific dimensions but also their personal, interpersonal aspects dimensions too. Page 119: Why is speculative ethics wrong? You should spell out what is your own ideal of ethics scholarship, otherwise you fall into crypto-normativism: you suggest implicitly a normative vision without spelling it out yourself. Throughout the thesis, there is no contextual analysis for the reasons/causes of speculation in ethics scholarship.	I appreciate Examiner 1's feedback on the depiction of speculation in this dissertation. I have added the following paragraphs on pages 106 to 108 of Chapter 3 to provide a richer description of speculative ethics, reasons and causes for speculation in ethics, and my perspective on how it fits into my own ideal of ethics scholarship: "Although Gilbert, Viaña, and Ineichen (2018) caution against unwarranted and unsubstantiated speculation on the effects of DBS on PIAAAS, we do not aim to disregard the role and importance of speculation. Speculation in bioethics involves an attempt to predict scenarios and draw conclusions on their possible outcomes based on assumptions that cannot be verified by present empirical or scientific claims. We acknowledge that through this effort, major ethical challenges can be foreseen before a novel technology or a new application of an existing technology is introduced and disseminated (Racine et al. 2014), allowing adequate steps to be taken to avert or deal with these challenges (Roache 2008). Furthermore, we agree with Roache (2008) that properly grounded and knowledge-based speculation (Racine et al. 2014) encourages ethical evaluation at the start or early stages of a project, helping avoid unethical or ethically misguided scientific endeavours before a significant amount of money, time, and careers has been invested in them. Speculation, even of future scenarios with low probabilities of occurring, could also be instrumental in motivating the conduct of crucial ethical projects (Roache 2008) that address present issues. Pragmatism's commitment to fallibilism (Arras 2002), acknowledging that knowledge is not absolute (Brown 2008), also signifies room for making speculations, as long as they follow a thorough review of empirical information (Fins, Bacchetta & Miller 1997; Fins 2005) and discuss the limitations of various methods in obtaining such information, as indicated

	in the paper of Gilbert, Viaña, and Ineichen (2018) and in one of the preceding paragraphs. With pragmatism's emphasis on scenario and context-based ethical deliberation (Fins, Bacchetta & Miler 1997; Racine 2008b), it is important to critically appraise previous speculations and conclusions made to see how well they still fit within a particular context and the extent of the applicability of any claims made. For instance, the article of Gilbert, Viaña, and Ineichen (2018) highlighted that "the prevalence and incidence of effects on PIAAAS might not be exclusively correlated with a specific DBS target and/or stimulation parameter. It should rather be seen as a result of the interaction between electrical stimulation, adjustments in medication, and natural progression of the disease" (p. 10, Gilbert, Viaña & Ineichen 2018). This claim underscores the significance of context in translating ethical claims. In addition to taking into account biological details of a case, it is essential to factor in family dynamics, institutional arrangements, social norms (Fins, Bacchetta & Miller 1997), cultural practices, and broader environmental factors that could affect the extent in which a person receiving DBS adjusts and adapts to DBS therapy. The applicability, importance, and relevance of any speculations made should be viewed from both techno-scientific and psycho-socio-environmental vantage points, considering not just the perspectives of people receiving DBS but also of the attending medical professionals and of family and caregivers. Finally, fallibilism should be applied to both qualitative and quantitative claims. Potential biases due to conflicts of interest (Bebbington 2003) and/or limitations and challenges in gathering comprehensive quantitative information (Fairchild et al. 2018) should be acknowledged when presenting and drawing claims from quantitative data. For instance, the applicability to ethical claims of prevalence rates of various psychiatric symptoms in people with Parkinson's disease indicated in the paper of Gilbert, Viaña, and Ineichen (2018) might be affected by location, time period, specific patient population, institutional capacities, and other socio-environmental factors that influence the reporting and diagnosis of psychiatric symptoms (Woodall et al. 2010; Kohrt et al. 2014)." With regards to Examiner 1's point on this dissertation being "premised on a rather narrow description of the problem addressed, often starting with technological development and clinical research with little integration of social context and relational aspects of situations experienced by patients and

	their relatives", I agree that the two publications in Chapters 4 (Viaña et al. 2017) and 5 (Viaña, Bittlinger, and Gilbert 2017) on ethical considerations on clinical trials of DBS for people with AD mainly gravitate towards techno-scientific details of the clinical trials. However, the publication in Chapter 6 (Viaña and Gilbert 2018) places great emphasis on the importance of personal and interpersonal aspects, with its use of the tripartite model of selfhood to hypothesise or speculate on the possible effects of DBS on self referencing, self-description, and relationality of people with Alzheimer's disease. I have also added the following sentences in this dissertation to further underscore the importance of getting the perspectives of multiple stakeholders and investigating ethical issues from both techno-scientific and psycho-social vantage pints: Chapter 3, page 107: "In addition to taking into account biological details of a case, it is essential to factor in family dynamics, institutional arrangements, social norms (Fins, Bacchetta & Miller 1997), cultural practices, and broader environmental factors that could affect the extent in which a person receiving DBS adjusts and adapts to DBS therapy. The applicability, importance, and relevance of any speculations made should be viewed from both techno-scientific and psycho-socio-environmental vantage points, considering not just the perspectives of people receiving DBS but also of the attending medical professionals and of family and caregivers." Chapter 3, page 108: "Furthermore, in order to apply a complete pragmatic approach (Fins, Bacchetta & Miler 1997; Racine 2008b) to investigating and understanding the ethical concerns associated with DBS for AD, deliberation with patients, family members and caregivers, researchers, and medical staff should be made using recommendations in this paper's three main publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) as guiding frameworks. This would ensure that ethical recommendations are actually enacted and evaluated, in addition to determining additional techno-scientific and psycho-socio-environmental factors, especially participant and caregiver actual lived experiences, that are crucial in developing more sound and adaptive

	recommendations for ongoing and future DBS for AD clinical trials."
There is no general imitations section, no acknowledgment of what was fulfilled and not fulfilled by the doctoral research project	I would like thank Examiner 1 for pointing this out. I have added the following paragraphs to provide a more concrete description of the goals and limitations of this dissertation: Chapter 1, pages 12 to 13: "At this point, it is also important to stress what this dissertation does not try to achieve. First, although pragmatic ethics focuses on the role of deliberation and negotiation (Fins, Bacchetta & Miller 1997; Racine 2008b), research for this dissertation does not include direct engagement with people participating in DBS for AD clinical trials, their family members and/or caregivers, and researchers and clinicians having an active role in the conduct of these trials, given that none of the trials are performed in Australia. As such, this dissertation employs a relatively limited pragmatic approach. Nevertheless, by drawing directly from information on how the trials are set-up and recruited, in addition to previous studies on clinical trials of DBS for other indications and on how Alzheimer's disease could affect selfhood and decision-making, this thesis embraces the pragmatic framework, at least to the extent in which it uses an interdisciplinary approach that acknowledges the contributions of medicine, social science, and philosophy to providing practical recommendations that would help guide the ethical conduct of ongoing and prospective DBS for AD trials. The three main publications in this thesis (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) could also serve as groundwork for future ethics research that employ a fuller pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b) – directly engaging with participants and researchers in DBS for AD trials, determining how the recommendations forwarded in the publications help improve the conduct of these trials, and gauging additional concerns of multiple stakeholders that warrant further moral reflection." Chapter 8, pages 247 to 249: "This dissertation draws insights from pragmatism (Fins, Bacchetta & Miller 1997; Racine 2008b) in order to propose recommendations that aim to improve the ethical conduct of clinical trials of DBS and other invasive neurotechnologies in people with AD. Although ethical reflection in this dissertation is based on empirical information from the results of DBS for

	AD clinical trials, animal studies evaluating the effects of fornix stimulation, studies on the impact of AD on selfhood, and information from research involving people who have received DBS for other conditions, the major limitation of this work is that there was no direct engagement with people with AD who have received DBS, their caregivers and/or family members, and researchers and health care personnel conducting the trials. As such, this thesis can only claim partial application of a pragmatic approach (Fins, Bacchetta & Miller 1997; Racine 2008b), considering the absence of engagement, deliberation, and negotiation with key stakeholders involved in this clinical research endeavour. To gauge the full spectrum of ethical concerns arising from clinical trials of DBS for AD, qualitative and quantitative studies must be performed on people with AD who have received or will receive DBS and their family members, caregivers, study partners, and/or surrogate decision makers, inquiring about their motivations and apprehensions for participating in a clinical trial; lived experience before, during, and after a DBS trial; and ethical and moral concerns faced during different trial stages. Interviews and surveys with researchers, scientists, doctors, and other medical professionals who are conducting DBS for AD trials and/or are involved in laboratory research relevant to this topic should also be performed. This will be crucial in acquiring a fuller understanding of the state of knowledge and research in this field; preliminary evidence on the potential safety and efficacy of DBS for AD beyond what is available in academic publications; motivations for pursuing this line of work in a vulnerable population, despite limited evidence; factors and considerations undertaken in participant recruitment, trial design, and selection of outcome measures; and personal reflection on possible ethical issues arising from the conduct of these clinical trials. To incorporate negotiation and deliberation (Fins, Bacchetta & Miller 1997; Racine 2008b), focus groups involving various stakeholders can be facilitated, allowing joint discussion on ethical issues from multiple perspectives and collaborative decision-making on possible ways in which they can be addressed. In these studies, a hypothesis-based approach could also be employed to determine how certain factors such as decision-making capacity of people with AD and their family members and possible conflicts of interest of researchers could influence their perceptions of ethical dilemmas and moral concerns arising from DBS for AD trials. Empirical studies are of crucial

	importance in this line of research, building upon the conceptual work presented in this dissertation. They would also provide an excellent opportunity to gauge whether the concerns and recommendations forwarded in the incorporated publications are similar to the ones voiced out by various parties, and on how can the recommendations be further improved to acknowledge contextual variations and the perspectives of multiple stakeholders. Although most publications presented in this dissertation performed a systematic search using specific keywords on various databases to survey empirical studies relevant to understanding ethical concerns in clinical trials of invasive neurotechnologies in people with AD, a more systematic review methodology following the PRISMA-P statement (Shamseer et al. 2015) could have been employed. This would facilitate increased transparency on the selection of animal studies, clinical trials on DBS for AD, and other empirical studies on people with AD or DBS recipients that are included in the publications and used to derive ethical recommendations. Furthermore, future ethics research on this topic could formulate and utilise a more concrete protocol in determining which occurrences during a clinical trial warrant serious consideration and an actual ethical recommendation. For the three main publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) in this dissertation, the requirements for ethical research trial forwarded by Emmanuel, Wendler, and Grady (2000) and elements essential in an ethics section of a clinical trial protocol, identified by Li et al. (2016), were used to direct the focus of the ethical analysis to participant selection, study design, and outcome measurement and reporting. In line with a pragmatic approach to bioethical analysis (Fins, Bacchetta & Miller 1997; Racine 2008b), deliberation with people with AD, family members, and healthcare personnel should be employed to determine what aspects in a DBS for AD clinical trial do they deem highly important and what results from previous studies would warrant more serious ethical reflection.”
Minor comments (typos, formulations)	
Suggestion/Feedback	**Response**
Missing “on-going” in “on practices and research involving” (page 18)?	I have already changed “on practices and research involving” on page 2 of Chapter 1 to “on on-going practices and research involving”.
“has written” and not “has wrote” (page 24)	I have already changed “has wrote” on page 18 of Chapter 1 to “have written”.

"these papers are" and not "these papers will" (page 24)	On page 18 of Chapter 1, I have already replaced "these papers will" with "these papers are".
"this chapter includes" and not "this chapter will include articles" (page 24)	I have already replaced "this chapter will include articles" with "this chapter includes articles" on page 18 of Chapter 1.
"also illustrates" instead of "will also illustrate" (page 25)	I have already changed "will also illustrate" on page 18 of Chapter 1 to "also illustrates".
Nuance the lack of advocacy for PET scan for diagnostic purposes given its (potentially hasty) admission in the USA (to differentiate between different forms of dementia? (page 33)	I greatly appreciate Examiner 1's recommendation of nuancing the lack of advocacy for PET scan in diagnosing AD and in differentiating it from other types of dementia. I have added the following points on page 27 of Chapter 2 in response to this suggestion: "Although FDG-PET ([^{18}F] fluorodeoxyglucose positron emission tomography) is already used in clinical practice to differentiate AD from other types of dementia, preventing the prescription of inappropriate medications for those with frontotemporal dementia or dementia with Lewy Bodies, the hasty and inappropriate use of amyloid imaging for AD diagnosis is cautioned against. A negative result on an amyloid PET scan indicates reduced likelihood of AD as the underlying cause of cognitive impairment; however, a positive result does not establish differential diagnosis between AD and other amyloid-beta disorders such as dementia with Lewy bodies or cerebral amyloid angiopathy (Marcus, Mena & Subramaniam 2014). Furthermore, a positive result may be incidental since cognitively-normal adults could also exhibit age-related increase in cerebral amyloid (Atri 2016). As such, when using amyloid PET imaging to aid in AD diagnosis, it is important that other clinical information are considered, standardized protocols are followed, and the procedure and scan interpretation are performed by staff and clinicians with expertise in neurodegenerative disorders (Marcus, Mena & Subramaniam 2014)."
Missing "not" in "was able to" on page 46	Upon double checking the paper of Sabat (2002), the woman referred to in this study was indeed still able to "refer to her previous ability to find the exact words for her thoughts, being a former academic, and shared her frustrations from not being able to use the most appropriate words as a result of AD (Self 2)." As such, there is no missing "not" in the phrase referred to.
Change "would be useful" for "will be useful" (page 51)	I have already replaced "would be useful" with "will be useful" on page 46 of Chapter 3.
Insert "the" in "for the informed consent procedure and the design of DBS..." (page 51)	I have already changed "for the informed consent procedure and design of DBS" on page 46 of Chapter 3 to "for the informed consent procedure and the design of DBS".

Why is the therapeutic use of electric stimulation not dated back to the Ancient civilizations (page 52) and actually to 1936-7	In this statement, I am referring to the modern way of using electrical stimulation for therapy. I have added "instrument-induced" in this sentence on page 47 of Chapter 3 to further clarify what I am referring to: "The first therapeutic application of instrument-induced electrical stimulation of the brain was reported in 1936 and in 1937 when it was used to localize the firing point for epilepsy (Penfield 1936) and in mapping cortical somatic motor and sensory representation (Penfield, Wilder & Boldrey 1937), respectively."
Does "leisure tourism" (page 61) stand for sex tourism? If that's the case it should be spelled out very transparently without any euphemism	Houeto et al. (2002) did not specify whether "leisure tourism" meant "sex tourism". As such, I would prefer not to elaborate further on this so as not to put my own words or interpretation on the researchers' own definition and conceptualization of "leisure tourism".
"to cross an international boarder" instead of "cross the border" (page 65)	I have already replaced "to cross the border" with "to cross an international border" on page 61 of Chapter 3.
Check syntax in "various qualitatively different kinds..." (page 66)	I have already changed "In this study, we demonstrated that there are various qualitatively different kinds" on page 62 of Chapter 3 to "In this qualitative study, we demonstrated that there are different kinds".
I wondered if the repeated statements "are included in this manuscript" (e.g., page 69, page 107, page 214 and so on) should not be changed to something like "are included in this thesis" or "are included in this doctoral dissertation"	I have already replaced all instances of "are included in this manuscript" with "are included in this doctoral dissertation".
page 77, not clear what the "#" stands for in the table	I have added the following statement on page 66 of Chapter 3 to state what the "#" in the paper of Gilbert et al. (2017) stands for: "Note: In the table on page 75, the "#" for the Model of Self employed in the studies of Gilbert (2013a, 2015, 2017) indicates that no particular model of the self was advocated for, given that these studies focus more on the concept of self-estrangement from a phenomenological point of view. I would like to thank one of the examiners for clarifying what was meant by this symbol in the table."
Typo in "[7]., etc." (page 109)	I have included the following sentences on page 109 of Chapter 3 to acknowledge the typographical error in the paper of Gilbert, Viaña, and Ineichen (2018):

	"Note: On page 111, there is a period after "has the potential to alter essential features of a patient's personhood, including mood, personality, and cognitive abilities [7]". This was a typographical error, and the period should not have been there. "[7]., etc." should be replaced with "[7], etc." I would like to thank one of the examiners for pointing out this mistake."
How do know that the "prevalence of evidence" was not biased by conflicts of interest" (page 117). Why are you so confident in the prevalence rates reported? (page 117)	Indeed, there is no way to directly know that the "prevalence of evidence" reported in the paper of Gilbert, Viaña, and Ineichen (2008) is not biased by conflicts of interest. As such, I am not completely confident with the prevalence rates reported. I have added the following sentences on pages 107 to 108 of Chapter 3 to reflect this stance: "Finally, fallibilism should be applied to both qualitative and quantitative claims. Potential biases due to conflicts of interest (Bebbington 2003) and/or limitations and challenges in gathering comprehensive quantitative information (Fairchild et al. 2018) should be acknowledged when presenting and drawing claims from quantitative data. For instance, the applicability to ethical claims of prevalence rates of various psychiatric symptoms in people with Parkinson's disease indicated in the paper of Gilbert, Viaña, and Ineichen (2018) might be affected by location, time period, specific patient population, institutional capacities, and other socio-environmental factors that influence the reporting and diagnosis of psychiatric symptoms (Woodall et al. 2010; Kohrt et al. 2014)."
Why "Nonetheless" in "Nonetheless, this study"? A pragmatic model of philosophy does not antagonize conceptual and empirical research (page 171).	I have already deleted the "Nonetheless" before "this study also acknowledges the richness" on page 173 of Chapter 7.
Change "more closely on peculiarities" to "more closely at peculiarities" (page 177)	I have already replaced "more closely on peculiarities" with "more closely at peculiarities" on page 180 of Chapter 7.
Change "Throughout the PhD" for "Throughout my doctoral research" (page 205)	I have already changed "Throughout the PhD" on page 208 of Chapter 7 to "Throughout my doctoral research".
Insert "project" after "A possible bioethical research" (page 209)	I have already replaced "A possible bioethical research concerning" with "A possible bioethical research project concerning" on page 212 of Chapter 7.
Provide a reference for the "applied and pragmatic ethical approach" (page 242)	I have added "(Fins, Bacchetta & Miller 1997; Racine 2008b)" after "a pragmatic ethical approach" on page 245 of Chapter 8.
Confusion between practical and pragmatic (page 242 and 244)	In Chapter 8, I have replaced "an applied and pragmatic ethical approach" with "a pragmatic ethical approach" on page 245. I have also replaced "pragmatic" with "practical" on page 249.

Responses to Examiner 2's comments and recommendations

Key areas for improvement	
Suggestion/Feedback	**Response**
It would be useful to include a brief section, or even simply a paragraph, that consists in a narrative about the methodology employed, in particular for the first two main publications. The justification for the choice of methodology (for example, versus a scoping or systematic review) as well as additional details about how and which publications were selected as part of the review would be critical to provide context for the body of work.	I would like to thank Examiner 2 for suggesting the inclusion of a paragraph on the search methodology I employed for the first two main publications. I have included the following paragraph on pages 10 to 11 of Chapter 1 to address this point: "Through the principle-guided pragmatic approach (Fins, Bacchetta & Miller 1997; Emanuel, Wendler & Grady 2000; Racine 2008b; Li et al. 2016) described in the preceding paragraphs, this dissertation critically examines the protocols of animal research and in-human trials of DBS for AD, determines aspects of these studies that necessitate ethical reflection, and provides recommendations that directly address ethical concerns arising from the recruitment, design, and conduct of these studies. Considering the emphasis placed by pragmatism on the contribution of scientific and clinical knowledge derived from empirical investigations to ethical debates (Fins, Bacchetta & Miller 1997; Racine 2008b), ethical reflection was based on the set-up and results of clinical trials and/or animal studies testing the effect of DBS on animal models or on people with AD. For the three publications that are the main focus of this dissertation (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018), past and ongoing trials of DBS in people with AD were determined using a PubMed and clinicaltrials.gov search of the keywords "DBS Alzheimer's disease" while completed animal studies that employed DBS of the fornix were identified using the keywords "DBS fornix" on PubMed. For the paper examining potential effects of DBS on the selfhood of people with AD (Viaña & Gilbert 2018), references were obtained through a search on PubMed, Scopus, and Google Scholar using the keywords "Alzheimer's disease", "dementia", "deep brain stimulation", "selfhood", "social constructionist", and "identity" and their corresponding permutations and combinations. Primary studies and case reports that explored the impact of AD on the social constructionist framework's three aspects of the self were identified and highlighted in this review. There were no studies that investigated the impact of DBS on selfhood using the social constructionist framework, so relevant studies that discussed its effects on self recognition and perception, psychological and psychiatric profiles, identity, and social adjustment were referenced instead. For the research involved

	in all three publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018), the references of highly relevant articles were also examined to expand the search coverage and identify other articles related to the initial keywords used. No specific period was set during the searches, and only articles that are fully in or with abstracts in English were included as references for the three publications." I have also described the limitations of the search method and review strategy I employed in the main publications included in this dissertation on pages 248 to 249 of Chapter 8: "Although most publications presented in this dissertation performed a systematic search using specific keywords on various databases to survey empirical studies relevant to understanding ethical concerns in clinical trials of invasive neurotechnologies in people with AD, a more systematic review methodology following the PRISMA-P statement (Shamseer et al. 2015) could have been employed. This would facilitate increased transparency on the selection of animal studies, clinical trials on DBS for AD, and other empirical studies on people with AD or DBS recipients that are included in the publications and used to derive ethical recommendations."
Within the section about methodology, I would invite the candidate to provide an indepth description of how the analytical framework was applied and how the recommendations were formed. As one example, for the recommendations about verifying if fornix stimulation triggers autobiographical memory as a marker of eventual therapeutic response – what methodology was employed to derive these recommendations from the literature? Which metrics were used to determine if an occurrence described in the literature warranted a recommendation?	I would like to thank Examiner 2 for inviting me to provide an in-depth description of the analytical framework I used. I have included a paragraph in pages 11 to 12 of Chapter 1 to describe in detail how I applied a pragmatic framework for the recommendations forwarded in the three main publications in this dissertation: "For the three main publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018), the pragmatic analytical framework (Fins, Bacchetta & Miller 1997; Racine 2008b) was employed to provide recommendations that acknowledge and address ethical concerns specifically arising from evaluating the safety and efficacy of DBS in people with AD. After obtaining relevant literature through methods detailed in the preceding paragraph, scientific papers describing the clinical trials of DBS for people with AD were carefully and critically read and details on different aspects of the trial such as inclusion and exclusion criteria, consent procedure, characteristics of the population enrolled, study design, and measured outcomes and results were placed in a Microsoft Excel matrix to facilitate better comparison among different trials. By using information on the pathophysiology,

	diagnosis, and prognosis (Fins, Bacchetta & Miller 1997) of AD and the mechanisms of action and possible risks of DBS, better assessment of the suitability of the enrolled participants and the design of the clinical trials could be made. With the focus of clinical pragmatism on patient's decision-making capacity and family dynamics (Fins, Bacchetta & Miller 1997), the way the informed consent was obtained for the trials and how the opinions of family members and caregivers were taken into account in the consent procedure, in addition to how AD could affect decision-making capacity, were also examined. In the identification of ethical considerations in the three major publications, institutional arrangements and broader social norms (Fins, Bacchetta & Miller 1997) were considered in identifying DBS access issues and in determining how social factors such as malignant positioning of people with dementia (Sabat & Collins 1999) and therapeutic misconception of invasive neurotechnological trial participation (Fisher et al. 2012) could affect the lived experience of a person with dementia who is receiving DBS. Furthermore, relevant moral considerations are also identified (Fins, Bacchetta & Miller 1997), highlighting potential tensions between the need to properly and systematically investigate an intervention that might be beneficial to people with AD and the obligation to ensure that vulnerable people with impaired-decision making are not taken advantage of and are not subjected to risky interventions with minimal possibility of benefit. With the focus of pragmatic ethics on suggesting goals of care (Fins, Bacchetta & Miller 1997) and on drawing from various disciplines to create new forms of wisdom in the pursuit of health (Racine 2008b), the ultimate aim of the three main publications in this dissertation (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) is to suggest plans of action that would minimise harm and ensure the welfare of clinical trial participants, ensuring that adequate care and respect are provided in the context of a clinical trial. Finally, clinical pragmatism advocates for periodic review and modification of course of action as the case evolves (Fins, Bacchetta & Miller 1997). As such, results from previous clinical trials of DBS for AD are also assessed to see how they can inform the design of ongoing and planned trials, ensuring that the participants enrolled and that the set-up of the clinical trials would lead to the greatest prospect of benefit and the least possibility of undue medical and social harms."

	On page 249 of Chapter 8, I have also mentioned limitations of the methodology I employed in deriving the recommendations forwarded: "Furthermore, future ethics research on this topic could formulate and utilise a more concrete protocol in determining which occurrences during a clinical trial warrant serious consideration and an actual ethical recommendation. For the three main publications (Viaña et al. 2017; Viaña, Bittlinger & Gilbert 2017; Viaña & Gilbert 2018) in this dissertation, the requirements for ethical research trial forwarded by Emmanuel, Wendler, and Grady (2000) and elements essential in an ethics section of a clinical trial protocol, identified by Li et al. (2016), were used to direct the focus of the ethical analysis to participant selection, study design, and outcome measurement and reporting. In line with a pragmatic approach to bioethical analysis (Fins, Bacchetta & Miller 1997; Racine 2008b), deliberation with people with AD, family members, and healthcare personnel should be employed to determine what aspects in a DBS for AD clinical trial do they deem highly important and what results from previous studies would warrant more serious ethical reflection." No specific established methodology was used to derive the recommendation on verifying if fornix stimulation triggers autobiographical memory is a marker of eventual therapeutic response (Viaña et al. 2017). This recommendation was made after reading the results of the Phase 1 trial (Laxton et al. 2010) showing that those who had experiential phenomenon during in-surgery stimulation had better cognitive outcomes from the trial. As such, I believe that verifying if this relationship indeed exists would help better tailor participant and brain target selection in future trials of DBS for AD.
During his thesis defense, I would recommend that the candidate explore how the same research questions could be addressed using a hypothesis-based approach.	I appreciate Examiner 2's suggestion of exploring how the research questions on the ethical issues raised by DBS for AD in this dissertation could be addressed using a hypothesis-based approach. There is no formal thesis defense at the University of Tasmania, so I have just included the following paragraphs on pages 247 to 248 of Chapter 8 of this dissertation to address this point and elaborate further how an empirical study involving stakeholders could be performed to determine ethical issues associated with invasive neurotechnological trials involving people with AD:

	"To gauge the full spectrum of ethical concerns arising from clinical trials of DBS for AD, qualitative and quantitative studies must be performed on people with AD who have received or will receive DBS and their family members, caregivers, study partners, and/or surrogate decision makers, inquiring about their motivations and apprehensions for participating in a clinical trial; lived experience before, during, and after a DBS trial; and ethical and moral concerns faced during different trial stages. Interviews and surveys with researchers, scientists, doctors, and other medical professionals who are conducting DBS for AD trials and/or are involved in laboratory research relevant to this topic should also be performed. This will be crucial in acquiring a fuller understanding of the state of knowledge and research in this field; preliminary evidence on the potential safety and efficacy of DBS for AD beyond what is available in academic publications; motivations for pursuing this line of work in a vulnerable population, despite limited evidence; factors and considerations undertaken in participant recruitment, trial design, and selection of outcome measures; and personal reflection on possible ethical issues arising from the conduct of these clinical trials. To incorporate negotiation and deliberation (Fins, Bacchetta & Miller 1997; Racine 2008b), focus groups involving various stakeholders can be facilitated, allowing joint discussion on ethical issues from multiple perspectives and collaborative decision-making on possible ways in which they can be addressed. In these studies, a hypothesis-based approach could also be employed to determine how certain factors such as decision-making capacity of people with AD and their family members and possible conflicts of interest of researchers could influence their perceptions of ethical dilemmas and moral concerns arising from DBS for AD trials. Empirical studies are of crucial importance in this line of research, building upon the conceptual work presented in this dissertation. They would also provide an excellent opportunity to gauge whether the concerns and recommendations forwarded in the incorporated publications are similar to the ones voiced out by various parties, and on how can the recommendations be further improved to acknowledge contextual variations and the perspectives of multiple stakeholders."
Minor comments	
Suggestion/Feedback	**Response**
The thesis would benefit from figures, in particular one on the potential mechanisms of action of deep brain stimulation and one	I have added a figure on page 25 of Chapter 2 and another figure on page 52 of Chapter 3 to illustrate the clinical

on the clinical features of Alzheimer disease progression, to aid in setting the context.	progression of AD and the mechanisms of action of DBS, respectively.
Studies of identity and selfhood in deep brain stimulation are often qualitative in nature as dictated by the research question, which can limit their representativeness as the candidate aptly points out in a statement on page 105. The candidate may wish to comment on the various biases researchers may encounter when conducting qualitative work (e.g., interview studies).	I have added a paragraph on page 104 of Chapter 3 to point out various biases researchers may encounter when they conduct qualitative work: "Considering that exaggerated claims can result from the overinterpretation and non-systematic analysis of cited empirical studies, it is important to acknowledge the limitations of qualitative empirical studies themselves that could also contribute to hyperinflated pronouncements. One of which is the possibility of bias in terms of the segment of the interview included in the paper, manifested as "cherry picking" of data presented in order to conform with a particular pre-established conceptual stance, hypothesis, or agenda of the researchers (Morse 2015; Galdas 2017). In addition, there could also be bias in the selection of the interviewees and in the formulation of questions, especially in the comparison of different interventions in samples that are likewise inherently non-equivalent. Though certain steps such as member checks and triangulation can be taken to lessen bias (Morse 2015), it is always important for qualitive researchers and those who cite their work to acknowledge inherent limitations of qualitative research in order to moderate the extent of any claims and conclusions."
The candidate should revise the introduction and discussion sections and eliminate the use of imprecise language (e.g., "has taken off", page 18).	I have revised the first sentence of Chapter 1, which can be found on page 2, to eliminate imprecise language and provide evidence for the claim made. "Neuroethics, a discipline encompassing both the ethics of neuroscience and neuroscience of ethics (Roskies 2002), has gained prominence in the past decade and a half, as evidenced by an increase in publications and research efforts and by the establishment of dedicated journals and academic societies (Racine et al. 2017; The Lancet Neurology 2018)."
In the current state of uncertainty in the quality of peer-reviewed journals, the candidate may want to define Q1 journals (page 20).	I have revised the clause on pages 13 to 14 of Chapter 1 to make what I meant by Q1 clearer: "which were also published in journals ranked by Scimago Lab to be in the first quartile of their respective subjects (Scimago Lab 2017)"
As some individuals with Mild Cognitive Impairment (MCI) do not convert to Alzheimer disease, I would suggest avoiding likening MCI to "pre-dementia" (page 32).	I have deleted "or MCI" before "phase of AD" on page 25 of Chapter 2 to address Examiner 2's suggestion.

	I have also added a sentence in the caption of Figure 1 on page 25 of Chapter 2 to further emphasise this point: "It is important to note that not all people with MCI (mild cognitive impairment) will progress to clinically-defined AD dementia (Frolich et al. 2017)."
In the introduction chapters, I would suggest moving the pathophysiology section ahead of the other topics, as there are discussions of A-beta and tau embedded into other sections (e.g., genetics) and it may be helpful for the flow of the thesis to describe and define these hallmarks first.	I have already moved the "Pathophysiology of Alzheimer's Disease" section ahead of the "Genetics of Alzheimer's Disease" section in Chapter 2.
I would encourage the candidate to reference the sentence that describes the benefits of Alzheimer disease drugs (page 41) as these are somewhat debated in the dementia research community.	I have added "(Anand, Gill & Mahdi 2014)" after "Monotherapy with these drugs has been shown to improve cognitive function, slow the pace of cognitive decline, and reduce behavioural symptoms" on page 35 of Chapter 2 to provide a reference for the statement made. I have also added "in people with mild to moderate AD (Tsoi et al. 2019)" after this sentence to highlight the limited benefit of monotherapy.

Once again, I would like to thank the two examiners for their feedback and suggestions for improvement of my doctoral thesis. I would also like to thank you in advance for the time that you will dedicate in ensuring that I have responded to the examiners' comments and have made corresponding changes to my PhD thesis. I hope that this manuscript would shed light on both recurring and novel ethical issues brought about by clinical trials of deep brain stimulation and other invasive neurotechnologies for people with Alzheimer's disease. Should you have further inquiries or clarifications, feel free to contact me, and I will try to address them as soon as possible.

Sincerely,

John Noel M. Viaña, M.Sc.
PhD candidate, University of Tasmania, Australia
Affiliate member, Ethics, Policy, and Public Engagement Program
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Cellphone Number: +61432741133

References (not in the dissertation but in this response to examiners' feedback):

Choi, BC & Pak, AW 2006, 'Multidisciplinarity, interdisciplinarity and transdisciplinarity in health research, services, education and policy: 1. Definitions, objectives, and evidence of effectiveness', *Clin Invest Med*, vol. 29, no. 6, pp. 351-364.

Appendix 4. Abstracts of poster and oral presentations

Conference: 11th Annual International Electromaterials Science Symposium

Venue: Deakin University, Melbourne, Australia

Date: February 10 to 12, 2016

Presentation type: Poster presentation

Enthusiastic Portrayal of 3D Bioprinting in the Media

John N Viana[1], Frederic Gilbert[1,2*] & Susan Dodds[1,2]

[1]*University of Tasmania*

[2]*ARC Centre of Excellence for Electromaterials Science*

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There has been a surge in media reports extolling the potential clinical potential for using 3D bioprinting to treat a wide range of conditions, with several clinical trials being undertaken. Implantable 3D-printed biomaterials are not free of ethical challenges as they can present severe risks of irrevocable harm to patients. Our study surveys key English-speaking media and determines whether there is a bias in favour of 3D Bioprinting in the media coverage. Medial dissemination of selective positive 3D bioprinting findings may mean that potential risk of harms are not appropriately brought to the attention of prospective experimental participants and increase the risk that researchers' may neglect significant ethical issues.

Conference: 10th FENS (Federation of European Neuroscience Societies) Forum of Neuroscience 2016

Venue: Bella Center, Copenhagen, Denmark

Date: July 2 to 6, 2016

Presentation type: Poster presentation

Ethical considerations for clinical trials of DBS for patients with Alzheimer's disease

Viaña JNM, Gilbert F

Alzheimer's disease is the most common form of dementia affecting more than 5.3 million people in the USA alone. FDA-approved drugs only provide temporary relief to memory problems, and no disease-modifying therapies are currently available. Recently, case reports and initial clinical trials on the potential use of DBS for memory improvement in people with Alzheimer's Disease or other neurologic conditions have been reported. In this poster, we examine ethical issues associated with performing experimental trials on DBS for people with Alzheimer's Disease in light of recent clinical and neuroscientific findings. In particular, we look at recently-published experimental trials of DBS of the fornix or of the nucleus basalis of Meynert in patients with mild probable to moderate Alzheimer's Disease. Exploring such trials allows us to identify and comprehend current ethical concerns, and anticipate potential issues for future trials of similar nature. We also suggest ideal clinical trial set-ups of DBS at different stages of AD that would ensure maximal protection of patients without compromising the scientific validity of experimental findings.

Conference: Neurizons 2016

Venue: Georg-August-Universität Göttingen, Göttingen, Germany

Date: May 31 to June 3, 2016

Presentation type: Poster presentation

Ethical considerations for DBS in patients with early-onset autosomal dominant Alzheimer's disease

Viaña JNM, Gilbert F

Alzheimer's disease is the most common form of dementia affecting more than 5.3 million people in the USA alone. FDA-approved drugs only provide temporary relief to memory problems, and no disease-modifying therapies are currently available. Although the cause of Alzheimer's Disease for most patients is multifactorial in nature, around 1% of people have early onset AD (EOAD) due to a rare autosomal dominant mutation in APP, PSEN1, or PSEN2. Recently, case reports and initial clinical trials on the potential use of DBS for memory improvement in people with Alzheimer's Disease or other neurologic conditions have been reported; however, none of them tested DBS on people with autosomal dominant EOAD. In this poster, we explore ethical considerations that must be undertaken when performing experimental DBS on people with autosomal dominant EOAD. While focusing on the best way to protect potential patients, we also examine the most appropriate kind of FDA approval that should guide such experimental trials and on how ethical guidelines would possibly differ from those in people where the onset of AD is at a later age.

Conference: University of Tasmania 2016 Graduate Research Conference

Venue: University of Tasmania, Hobart, Australia

Date: September 1 to 2, 2016

Presentation type: Poster presentation

Ethical Implications of Novel Neurotechnologies for Alzheimer's disease

John Noel M. Viaña[1,2] and Frederic Gilbert[1,2]

[1]Ethics, Policy and Public Engagement Program, Australian Research Council Center of Excellence for Electromaterials Science

[2]Philosophy and Gender Studies Program, School of Humanities, University of Tasmania

Alzheimer's disease is the most common form of dementia affecting more than 5.3 million people in the USA alone. FDA-approved drugs only provide temporary relief to memory problems, and no disease-modifying therapies are currently available. Recently, a number of neuroscience discoveries and inventions have shown potential to address Alzheimer's disease. These include deep brain stimulation, stem cell implantation, gene therapy, and optogenetics. Although these technologies could potentially provide improved management or even treatment of Alzheimer's disease, they are invasive in nature and thus, pose a number of medical risks to patients. Moreover, given that a majority of people affected by Alzheimer's Disease are old and demented, ethical concerns arise when novel treatments are tested and used in a vulnerable population with potentially limited ability to consent. This poster provides a brief overview of these four neurotechnologies and introduces the framework that will be used to examine associated ethical concerns for first in-human studies and clinical trials involving them. Although DBS, stem cells, gene therapy, and optogenetics

might offer additional therapeutic modules for AD, the ethical, scientific and clinical groundwork that need to be established have to be first elaborated before any of these highly invasive procedures that target a vulnerable group of patients are approved and recommended for wide use.

Conference: 2017 Sherwin B. Nuland Summer Institute in Bioethics (organized by the Yale Interdisciplinary Center for Bioethics) Student Poster Presentation

Venue: Medical Historical Library, Yale School of Medicine, New Haven, Connecticut, USA

Date: July 21, 2017

Presentation type: Poster presentation

Ethical considerations in patient selection and informed consent for Alzheimer's disease *in vivo* gene therapy trials

John Noel M. Viaña

Ethics, Policy and Public Engagement Program, Australian Research Council Center of Excellence for Electromaterials Science; Philosophy and Gender Studies Program, School of Humanities, Faculty of Arts and Law, University of Tasmania

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Abstract

Alzheimer's disease is the most common form of dementia affecting more than 5.3 million people in the USA alone. FDA-approved drugs provide only temporary relief to memory problems, and no disease-modifying therapies are currently available. Recently, results of the first in-human experimental trial involving *in vivo* gene therapy in people with Alzheimer's disease have been published. In this paper, I examine ethical issues associated with the experimental trial involving virus-mediated delivery of the nerve growth factor (NGF) gene to the nucleus basalis of Meynert of people with Alzheimer's disease. Specifically, I examine ethical concerns related to patient selection and recruitment, assessing if trial participants are indeed those who would potentially benefit the most and would have the

least amount of risks and harms. I also evaluate the informed consent procedure implemented. In general, I believe that the study should have recruited participants only of a very mild disease stage and should have also expanded their exclusion criteria to those with psychiatric abnormalities. Furthermore, the description of the informed consent process should have explicitly stated the involvement of the participant's caregiver and/or family, in addition to requiring that all participants have adequate capacity to understand the trial procedure and provide an informed, rationalized, and stable consent. These recommendations have to be taken into account in subsequent trials to ensure maximal protection of patients while maintaining the scientific validity of experimental findings.

Conference: International Neuroethics Society – 2017 Annual Meeting

Venue: American Association for the Advancement of Science Building, Washington, DC, USA

Date: November 9 to 10, 2017

Presentation type: Poster presentation

Ethical Considerations for Cell Implantation in Alzheimer's Disease

John Noel M. Viaña (J.N.M. Viaña)[1,2], Judy Illes (J. Illes)[2,3], Frederic Gilbert (F. Gilbert)[1,2,3]

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[2] National Core for Neuroethics, Faculty of Medicine, University of British Columbia, Vancouver, Canada

[3] Center for Sensorimotor Neural Engineering, Department of Philosophy, University of Washington, Seattle, USA; Tel: 1 203-616-5763

Alzheimer's disease is the most common form of dementia affecting more than 30 million people worldwide. FDA-approved drugs only provide temporary relief to memory problems, and no disease-modifying therapies are currently available. A number of studies testing different cell implantation strategies in Alzheimer's disease animal models have already been conducted (Tong, Fong, and Huang 2015, Emerich et al. 2014). A clinical trial has also investigated encapsulated cells delivering nerve growth factor to the basal forebrain in people with Alzheimer's disease (Eriksdotter-Jonhagen et al. 2012, Wahlberg et al. 2012). Currently, there are several clinicaltrials.gov-indexed in-human trials that evaluated or are

evaluating stereotactic brain injection of stem cells. In this study, we examine ethical issues associated with these invasive neurological studies in light of recent clinical and neuroscience findings in both humans and animal models, focusing on trial methodology and translational aspects (Viaña et al. 2017). In particular, we compare and contrast different cell implantation strategies used in past and ongoing trials, and identify ethical concerns related to translation justification, patient selection and recruitment, trial design, and treatment outcomes. We conclude with recommendations for ongoing and future trials to ensure maximal protection of patients without compromising the scientific validity of experimental findings.

Disclosure of Conflict/(s) of Interest: The authors have no conflict of interest to disclose.

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Viaña, J. N. M., J. C. Vickers, M. J. Cook, and F. Gilbert. 2017. Currents of memory: recent progress, translational challenges, and ethical considerations in fornix deep brain stimulation trials for Alzheimer's disease. *Neurobiol Aging* 56:202-210. doi: 10.1016/j.neurobiolaging.2017.03.001.

Conference: Neuroscience 2017 (Society for Neuroscience 2017 Annual Meeting)

Venue: Walter E. Washington Convention Center, Washington, DC, USA

Date: November 11 to 15, 2017

Presentation type: Poster presentation

Theme J: History and Education (J.04.a. Ethical and policy issues in neuroscience)

Ethical considerations for gene therapy in people with Alzheimer's disease

John Noel M. Viaña[1] and Frederic Gilbert[2]

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Alzheimer's disease is the most common form of dementia affecting more than 5.3 million people in the USA alone. FDA-approved drugs only provide temporary relief to memory problems, and no disease-modifying therapies are currently available. Recently, results of the first in-human experimental trials involving *in vivo* gene therapy in people with Alzheimer's disease have been published. In this poster, we examine ethical issues associated with these trials in light of recent clinical and neuroscientific findings. In particular, we look at experimental trials involving stereotactic adeno-associated virus-mediated delivery of the nerve growth factor (NGF) gene in people with Alzheimer's disease. We identify ethical concerns related to translation justification, patient selection and recruitment, trial design,

and treatment outcomes. Examining these issues allows us to understand pressing ethical and regulatory obstacles, and provide recommendations for ongoing and future trials of similar nature to ensure maximal protection of patients without compromising the scientific validity of experimental findings.

Conference: Asia-Pacific Centre for Neuromodulation 2017 Deep Brain Stimulation Symposium

Venue: Queensland Brain Institute, University of Queensland, Brisbane, Australia

Date: November 24 to 25, 2017

Presentation type: Oral presentation

Currents of memory: the ethics of deep brain stimulation for Alzheimer's disease

John Noel Viaña[a] and Frederic Gilbert[a,b,c]

[a]Ethics, Policy, and Public Engagement Program, Australian Centre for Electromaterials Science, University of Tasmania, Hobart, Australia

[b]Department of Philosophy and Center for Sensorimotor Neural Engineering, University of Washington, Seattle, USA

[c]National Core for Neuroethics, University of British Columbia, Vancouver, Canada

Currently, several clinical trials of fornix or nucleus basalis of Meynert (NBM) stimulation have been performed to treat memory and cognitive impairments associated with Alzheimer's disease (AD). These studies have tested the safety and the efficacy of deep brain stimulation (DBS), with results showing potential memory improvements depending on the age of the patient. This talk aims to provide a brief overview of the progress of DBS trials for AD and raise salient ethical concerns regarding patient selection, informed consent, study design, outcome evaluation, and result presentation and interpretation. It will also highlight several issues in recruiting people with early-onset Alzheimer's disease (EOAD), given the Phase II trial results showing that this group of patients could actually have worse cognitive outcomes post-DBS. This could be further complicated by the high prevalence of highly

penetrant autosomal-dominant mutations in this sub-group, which could affect prognosis and the rate of cognitive decline. This talk will then emphasize the need for adaptive strategies to minimize harms when recruiting people with EOAD and address issues arising from patient privacy and disclosure of genetic test results. Overall, recommendations will be provided to ensure that both people with early-onset and late-onset AD participating in DBS trials are well-protected, respected, and not subjected to undue harms.

Conference: Herrenhausen Conference: Lost in the Maze? Navigating Evidence and Ethics in Translational Neuroscience

Venue: Herrenhausen Palace, Hanover, Germany

Date: February 14 to 16, 2018

Presentation type: 1 poster presentation and 1 oral presentation

How does your approach specifically tackle the questions and challenges emerging from the field? Why should we select your project? (600 characters)

We use an empirical bioethics approach to identify ethical issues on invasive brain surgery for Alzheimer's (AD) trials, reviewing reports in academic journals and clinical trial databases. We examine issues on patient selection, informed consent, study design, and outcome measures. We also examine relevant animal studies to determine what valuable information can be derived from them and how applicable they are to human trials. Addressing these ethical issues, focusing on the justifiability of initiating in-human trials, directly benefits translational research protocols for AD treatment.

Men before mice: invasive brain stimulation trials for Alzheimer's disease

Authors: John Noel M. Viaña and Frederic Gilbert

There is concerning evidence showing that invasive brain surgeries to tackle Alzheimer's disease (AD) symptoms are increasingly being tested in humans despite being highly experimental, supported by little pre-clinical studies, and potentially bearing irreversible consequences to vulnerable patients. For instance, the serendipitous discovery of stimulation-induced autobiographical recollection and eventual verbal and spatial memory

improvements in a single patient treated with fornix deep brain stimulation (DBS) for obesity has precipitously led to several Phase I and Phase II trials for AD. Although DBS has been proven to be relatively safe in other trials, it is ethically intriguing how experimental AD trials were launched despite absence of pre-clinical data from animal models, which is the common practice for drug-based interventions. Does the approval and widespread use of subthalamic DBS for Parkinson's disease enough to justify testing of fornix DBS for AD? Are there special considerations when testing this kind of invasive brain intervention in a population with an impaired ability to consent? Finally, what role do animal studies play, and how applicable is the information obtained from them to trials in humans?

This presentation explores and addresses these questions by first reviewing the timeline of in-human and animal studies on fornix DBS for AD. Then, potential arguments for and against directly conducting a Phase I trial in humans from an outcome in a single case study for a different condition will be enumerated. The need for studies in animals before conducting a Phase I trial will be determined using perspectives based on the principles of beneficence, non-maleficence, and justice. The concept of 3R's (Replace, Reduce, Refine) will also be used to examine whether it is justifiable to directly conduct a Phase I trial and not investigate this intervention first in appropriate rodent and primate models of AD. Through these, we could better determine whether it is justifiable and ethical to have tried fornix DBS for AD on men first before conducting an extensive investigation of the safety and efficacy of this treatment modality in mice.

Conference: European Forum Alpbach 2018

Venue: Congress Centrum Alpbach, Alpbach, Austria

Date: August 15 to 31, 2018

Presentation type: Dance and verse choir presentation

Proposal for the International Evening Presentation at the 2018 European Forum Alpbach

John Noel M. Viaña, PhD student at the University of Tasmania

Performed by: John Noel M. Viaña, Dorel Butaciu, Mert Ceylan, Dorotea Neuberg, Theresa Ratheiser, Barbara Röhrer, Alieu Sowe, Rares Tracicaru, Phong Vu Dinh

Proposed pair of topics: Science and ethics

Title: **Delving deeper into brain stimulation narratives: communicating ethical discourse through dance and verse choir**

Scientific and technological developments have led to the improvement of the lives of countless individuals. However, some of the final products of science have actually caused distress to people and a reduction in their quality of life. Even for scientific fruits that have been approved for general use and have benefitted many people, some sub-populations did not benefit or were even harmed either by the final product itself or during the process of its testing, evaluation, and refinement.

Due to atrocities committed in the past such as mistreatment of vulnerable populations (African-Americans, children, etc.) in clinical studies and drug trials and crimes committed during World War 2 in the name of science and discovery, bioethics has been developed and

formalized as a discipline. Today, it continues its role in analysing issues that arise from developments in biology and medicine and helping ensure that no populations are exploited or unduly harmed by scientific innovations.

My PhD thesis focuses on issues arising from deep brain stimulation (DBS), a procedure wherein leads are inserted deep into a person's brain to transmit electrical currents and provide relief from motor or psychiatric symptoms that he or she is experiencing. DBS is approved in the USA, Europe, and in many other countries for use in people with Parkinson's disease and other motor disorders such as essential tremor and dystonia.

Although many people with Parkinson's have been able to better function as a result of DBS, with a number even being able to pursue professional activities or continue hobbies, a portion of individuals have developed unintended psychiatric symptoms or even felt self estrangement after DBS. Some people developed mania and/or hypersexuality, felt much stronger and attempted to do things beyond their physical capacity, and experienced marital conflicts and difficulties in social re-integration.[1-3]

This presentation would focus on results from empirical studies[3,4] where I was involved in and also from my ethical reflections[5] on clinical trials on new DBS indications. The empirical studies present narratives of people with Parkinson's disease who received deep brain stimulation. Some of the interviewees developed psychiatric symptoms and experienced problems coping with them. The studies detail how they dealt with these symptoms, coped with them, and even used them to create art. [3,4] The ethical reflections would focus on the possible effects of DBS on people with Alzheimer's disease (AD) and on how it could affect

different aspects of their selfhood, basing on the results of clinical trials of DBS for Alzheimer's and other indications, and on the impacts of memory loss and cognitive deficits in people with AD on their selfhood. These reflections reflect on how DBS could potentially allow people with AD to better appraise themselves and recall salient life events, but it also raises the possibility of people remembering repressed traumatic memories and being expected to fulfil tasks that they still would not be able to due to the small degree of memory improvement.[5]

The ideas raised and narratives shared in manuscripts in which I have contributed to will be presented in the form of dance and of interpretative and loud reading of passages from these texts.[3-5] I have tried choreographing some dance before to portray changes experienced by some people with Parkinson's as a result of DBS, and I would like to incorporate some ideas from that previous performance to the presentation during the international evening. Having other people join in the dance performance and reading of the texts would also result to a more elaborate and artistic presentation. The presentation would probably start with part of the group reading an introduction on DBS, Alzheimer's, and Parkinson's, and another part interpreting those passages through action and dance. Then, we will move on to demonstrate through body movement the possible unintended side effects of DBS for Parkinson's and how someone copes with them. Finally, some of the ethical reflections on the effects of DBS for Alzheimer's will be read aloud and with emotion, and potentially, also interpreted through dance and action.

Overall, this performance aims to communicate pressing ethical issues that accompany medical advancements, focusing on the lived experience of the technology's end users. Only by opening the ethical discussions and emphasizing that certain individuals might not fully

benefit from or even be harmed by an intervention can we fine tune technologies and develop strategies to make sure that people are well informed of the risks of a trial and treatment and also to better anticipate, mitigate, and minimize harms that end-users and their family might experience.

References:

1. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002; 72(6): 701-7.

2. Agid Y, Schupbach M, Gargiulo M, et al. Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so? Journal of neural transmission Supplementum 2006; (70): 409-14.

3. Gilbert F, Goddard E, Viaña JNM, Carter A, Horne M. I Miss Being Me: Phenomenological Effects of Deep Brain Stimulation. AJOB Neurosci 2017; 8(2): 96-109.

4. Gilbert F, Viana JN. A Personal Narrative on Living and Dealing with Psychiatric Symptoms after DBS Surgery. Narrat Inq Bioeth 2018; 8(1): 67-77.

5. Viana JNM, Gilbert F. Deep brain stimulation for people with Alzheimer's disease: Anticipating potential effects on the tripartite self. Dementia (London, England) 2018: 1471301218761147. Available from: http://journals.sagepub.com/doi/abs/10.1177/1471301218761147

Conference: 19th Asian Bioethics Conference

Venue: Open University of Kaohsiung and Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Kaohsiung, Taiwan

Date: November 13 to 16, 2018 (abstract for oral presentation accepted; forthcoming)

Presentation type: Oral presentation

Clinical trials of invasive neurotechnologies for dementia: an Asian perspective

John Noel M. Viaña

Philosophy and Gender Studies Program, School of Humanities, College of Arts, Law, and Education; Wicking Dementia Research and Education Centre, College of Health and Medicine; and Ethics, Policy, and Pubic Engagement Program, Australian Research Council Centre of Excellence for Electromaterials Science, University of Tasmania

The increase in the world's aging population implies that more and more people will be at risk for dementia, especially due to Alzheimer's disease. In the Asia Pacific region alone, at least 23 million people have dementia. Considering the lack of a cure and the health and economic burden to individuals and society brought by dementia, there is an ethical requirement and imperative to explore novel therapeutic modalities. A number of the modalities being tested in humans include deep brain stimulation and cell implantation. These neurotechnologies are highly invasive and pose a risk of harm greater than most conventional pharmacologic agents. As such, clinical trials involving these technologies raise salient ethical concerns. This talk would first present the current state of stem cell and deep brain stimulation clinical trials for dementia in Asia. It will then compare the trial design and enrolment criteria of trials conducted in Asian countries to those conducted in Europe and

North America. Second, it will enumerate possible ethical gaps in the clinical trials being conducted in Asian countries and provide recommendations for future trials to better protect trial participants and adequately inform them of possible risks and benefits. Finally, it will explore how clinical trials can be made more just, especially for the first participants, where there is less information on prospective benefits and trial-associated harms. By then broadening the lens to social justice, this talk will reflect on challenges that invasive neurotechnologies could face with regards to widespread application, should they get approved. Since a significant number of Asians with dementia are already being enrolled in clinical trials for invasive neurotechnologies, it is becoming increasingly important to address associated ethical issues using Asian perspectives on elderly care responsibility and healthcare resource allocation.

Conference: Australasian Society for Philosophy and Psychology 2018 Meeting

Venue: Macquarie University, Sydney, Australia

Date: December 5 to 7, 2018 (abstract for oral presentation accepted; forthcoming)

Presentation type: Oral presentation

Stimulating the brain or altering the self? The effects of neurostimulation for Alzheimer's disease

John Noel M. Viaña[1,2,3] and Frederic Gilbert[2,3,4]

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Alzheimer's disease (AD) leads to memory dysfunction and cognitive impairments, which have been shown to drastically affect the selfhood of afflicted individuals. Novel neurostimulation technologies tested to treat AD, such as deep brain stimulation, have also been associated with influencing the selfhood in different cohorts of patients (Parkinson's disease, Obsessive Compulsive Disorder, etc.), both due to their beneficial and potential adverse side effects. Considering the risks and irreversibility of these neurostimulative modalities, it is critical to anticipate how new neurostimulative interventions may affect self-related concepts in a population whose selfhood is already threatened by the cognitive,

psychological, and social implications of an AD diagnosis. Using DBS for AD as a case, we anticipate these potential effects through the lens of an extended social constructionist grounded tripartite model of selfhood, originally proposed by Harre and Sabat. By reconciling information from medical reports, psychological, philosophical, and sociological investigations on the impacts of DBS or AD on selfhood, we examine potential effects of DBS for AD on Self 1 or singularity through use of first-person indexicals, and gestures of self-reference, attribution, and recognition; Self 2 or past and present attributes, knowledge of these characteristics, and continuity of narrative identity; and Self 3 or the relational and social self. Anticipating these effects is crucial in ensuring adequate ethical oversight on informed consent procedures and care provision for people with AD enrolled or interested in enrolling in trials involving an invasive neurostimulation technology.

Appendix 5. Curriculum vitae of candidate

John Noel M. Viaña

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Applying for: Completion of a PhD in Neuroethics (Society and Culture) at UTAS

Career Overview

I am a PhD student in Society and Culture (Neuroethics) at the University of Tasmania and have just submitted my PhD thesis on the ethics of clinical trials on invasive neurotechnologies for Alzheimer's disease. I have a NEURASMUS Erasmus Mundus master's degree in Neurosciences from the Université de Bordeaux and Vrije Universiteit Amsterdam and a bachelor's degree in Molecular Biology and Biotechnology from the University of the Philippines Diliman where I graduated *cum laude*. In addition, I was a visiting researcher at the Brocher Foundation and a visiting student in neuroethics at Monash University, University of British Columbia, University of Washington, and Charité - Universitätsmedizin Berlin. I have also completed the 2017 Sherwin B. Nuland Summer Institute in Bioethics at Yale University. I have teaching and mentoring experiences through my roles as a career peer; tutor for Aboriginal and Torres Strait Islander students and tutor in Nursing Ethics and Good Thinking units at the University of Tasmania; intern at Yale University; and research associate at the University of the Philippines Diliman.

Education and Training

- **Visiting researcher:** Fondation Brocher**,** Geneva, Switzerland (September to October 2018)
  Project title: Invasive brain technologies for Alzheimer's disease: common concerns and novel considerations
- **Participant and scholar:** European Forum Alpbach 2018, Alpbach, Austria (August 2018)
  Courses/Seminars taken: Artificial Intelligence and Ethics; Our Work in Our Future; Technische Universitäten Austria Innovation Marathon; Health, Technology, Political, Legal, Economic, and Financial Market symposia
- **Visiting researcher/ PhD student:** Neuroscience and Society Group, Brain and Mental Health Laboratory, School of Psychological Sciences, Monash University, Australia (November 2017 to January 2018)
- **Visiting International Research Student:** Neuroethics Canada, Department of Medicine, University of British Columbia, Canada (September to October 2017)
  Courses/Seminars taken: Gene Therapy; Science Communication: The Crash Course
- **Short-term visiting PhD student:** Department of Philosophy and Center for Sensorimotor Neural Engineering, University of Washington, USA (August 2017)
- **2017 Sherwin B. Nuland Summer Institute in Bioethics student:** Yale Interdisciplinary Center for Bioethics, Yale University, USA; *awarded with a full tuition waiver* (June to July 2017)
  Courses/Seminars taken: Foundations in Bioethics; Bioethics and the Law; Bias in Bioethics; Personhood and Personal Identity in Bioethics; Environmental Ethics; Biotech Law and Patent Issues: The Global Biotech Business; Bioethics and the Media; LGBT Bioethics; Neuroethics; Ethical Issues in Psychiatry and Child Psychiatry; Bioethics Morning Lectures; Field trips to the Yale Medical History Library, Hastings Center, and the Connecticut Hospice;
  Final writing output and poster presentation: Ethical considerations in patient selection and informed consent for Alzheimer's disease *in vivo* gene therapy trials
- **Visiting PhD student:** Neurophilosophy, Medical Ethics, and Neuroethics Group, Division of Mind and Brain Research, Charité - Universitätsmedizin Berlin, Germany (June 2016)

- **PhD in Society and Culture (Neuroethics) and Graduate Certificate in Research:** University of Tasmania, Australia; Course GPA: 7.0/7.0; *Tasmania Graduate Research Scholarship* (September 2015 to Present)
  Expected graduation date: March 2019 (thesis submitted on October 12, 2018)
  Courses/Seminars taken: Introduction to Higher Degree by Research; Communicating Research; Introduction to Epidemiology; Health Economics; Certificate in Science Communication (ACES); Understanding Dementia; Preventing Dementia; Neuroscience and Society reading group (through Monash University); Unsettling the Humanities reading group; Queering Health reading group
  PhD thesis: Ethical considerations for deep brain stimulation and other invasive neurotechnological trials in people with Alzheimer's disease
  Dissertation description: This thesis examines studies on deep brain stimulation in people with Alzheimer's disease, reviewing clinical trials and relevant animal studies to highlight pressing ethical concerns that ongoing and forthcoming trials need to address. By having three major publications during the course of the PhD as the main chapters, this thesis aims to enumerate ethical issues that encompass the neurobiological and genetic, cognitive, individual, and societal dimensions of deep brain stimulation for Alzheimer's disease. These ethical considerations can then be extended into other forms of novel neurosurgical trials such as cell implantation and gene therapy.
- **NEURASMUS Erasmus Mundus Master's in Neuroscience (Neurobiology and Neurogenetics track):** VU University Amsterdam, Netherlands (1st year): Research Master's in Neurosciences; University of Bordeaux, France (2nd year): Master's in Biology, specialty in Neurosciences and Neuropsychopharmacology, mention *assez bien*; *Erasmus Mundus Category A Scholarship (*August 2013 to August 2015)
  Courses/Seminars taken: From Molecule to Mind (overview of cellular and molecular neuroscience, neuroanatomy, statistics; readings in neurophysiology; and lectures on the four major research themes – Attention and Cognition, Addictive Behavior, Anxiety and Depression, and Neurodegeneration at the Neuroscience Campus Amsterdam); Clinical Neurosciences; Behavioral Genetics; Neurogenomics; Scientific Writing in English; Cellular and Molecular Neurobiology; Techniques in Behavioral Experiments; Principles of Microscopy; Dynamic Imaging; Nonlinear Optics; Industrial Research
  First year research internship: Adeno-associated virus 2 and 5-mediated structural and GCaMP6-facilitated functional elucidation of cholinergic projections from the basal forebrain to the medial prefrontal cortex
  Master's thesis: Role of the ventral tegmental area (VTA) to medial prefrontal cortex (mPFC) dopaminergic projections during the acquisition of fear behavior
- **Bachelor of Science in Molecular Biology and Biotechnology:** University of the Philippines Diliman, Philippines; graduated c*um laude (*June 2008 to April 2012)
  Courses/Seminars taken: Algebra and Trigonometry; Calculus; Statistics; Biology (with laboratory); General, Analytical, Organic, and Biological Chemistry (with laboratory); Physics (with laboratory); Ethics in Scientific Research, Undergraduate Seminar in Molecular Biology and Bioenterprise; Molecular Biology and Biotechnology (Molecular Microbiology, Animal and Plant Cell and Tissue Culture, Molecular Physiology of Eukaryotic Systems, Molecular Genetics, Molecular Biophysics, Principles of Gene Manipulation, Genes and Development, Cellular and Molecular Immunology, and Industrial Biotechnology); General Psychology
  Undergraduate thesis: Evaluation of sodium alginate as a three-dimensional scaffold for neural cultures

Relevant Employment History

- **Tutor for the *Foundations for Professional Practice 2* unit (CNA1503):** *Philosophy and Gender Studies Program, School of Humanities, University of Tasmania, Australia (July to August 2018)*
  - Conducted two-hour tutorial sessions per week for four weeks for three groups of nursing students. Topics discussed include an introduction to ethics, acknowledging personhood and exercising person-centred approaches to negotiating care, and an introduction to the Australian medico-legal system
  - Marked and provided feedback to student presentations

- **Tutor for the *Good Thinking: Reasoning Skills for Life* unit (XBR105):** *Philosophy and Gender Studies Program, School of Humanities, University of Tasmania, Australia (March to June 2018)*
  - Moderated an online discussion group for 61 students, providing feedback on student posts and directing them to the correct answer to weekly questions regarding the topics discussed (clarifying reasoning, including mapping and standardisation of arguments; communicating reasoning; and evaluating reasoning, including discussions on general fallacies, deductive reasoning, and inductive reasoning)
  - Marked and provided feedback to student submissions (portfolios, essays, final exam)
- **Graduate Academic Tutor**: *Riawunna Centre for Aboriginal Education, University of Tasmania, Australia (March to May 2018)*
  - Provided academic support to Aboriginal and Torres Strait Islander students, helping them with the units (such as HGA101: Sociology A) they are taking and ensuring successful outcomes
- **Summer Intern:** *2017 Sherwin B. Nuland Summer Institute in Bioethics, Yale Interdisciplinary Center for Bioethics, Yale University, USA (May to July 2017)*
  - Welcomed students to the program and provided assistance in setting up online accounts, obtaining an ID card, and getting around the Yale campus
  - Facilitated three introductory bioethics discussion sessions to help international students be more comfortable with communicating in English
- **Research Assistant/ Researcher:** *Philosophy and Gender Studies Program, School of Humanities, University of Tasmania, Australia (July 2015 to Present)*
  - Conduct literature survey on explantation of brain implants, questionnaires to assess brain-computer interface outcomes, and representations of "cyborgs" in the philosophical literature
  - Assist in formatting references for article submissions to journals
  - Perform media research on 3D bioprinting using Factiva and present media trends using tables and graphs
  - Summarise important findings in primary and review papers on 3D bioprinting, with special emphasis on the safety and other ethical considerations for clinical trials involving 3D-printed biomaterials and biological units
  - Summarise and graph the status of PubMed-indexed publications and WIPO-indexed patents involving 3D bioprinting
- **University Research Associate I:** *Laboratory of Molecular and Cell Biology, National Institute of Molecular Biology and Biotechnology, University of the Philippines Diliman, Philippines (January to June 2013)*
  - Oversaw research projects being conducted at the laboratory and assisted in supervising undergraduate students and apprentices, teaching them laboratory techniques and helping them revise their thesis
  - Organised a three-week workshop on molecular and cell biology techniques to incoming students
  - Managed laboratory equipment, reagents, finances, and rodent strains
  - Assisted the project investigator in writing project reports and grant proposals and in presenting the laboratory's research to a wide range of audience
- **Secretary:** *Institutional Animal Care and Use Committee, University of the Philippines Diliman, Philippines (January to May 2013)*
  - Organised regular committee meetings and prepared necessary documents prior to and after each meeting
  - Coordinated with committee members from different institutes and departments at the university regarding animal housing and experimentation permit applications, regulatory approvals, and quality assurance of animal housing facilities

Additional Work and Research Experience

- **Concierge:** *Student Services and Information Centre, University of Tasmania, Australia (February to July 2018)*
- **Career Peer:** *Student Leadership, Career Development, and Employment team, University of Tasmania, Australia (February 2016 to May 2017)*
- **Graduate Researcher:** *Neuronal Circuits of Associative Learning team, INSERM U862, Neurocentre Magendie, France (September 2014 to June 2015)*
- **Research Intern:** *Department of Integrative Neurophysiology, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, Vrije Universiteit Amsterdam, the Netherlands (February to August 2014)*
- **Research Intern/Volunteer:** *Marine Science Institute, University of the Philippines Diliman, Philippines (September to November 2012)*
- **Academic Tutor:** *Ahead Learning Systems, Inc., Quezon City, Philippines (June to November 2012)*
- **Undergraduate Researcher/ Research Apprentice:** *Laboratory of Molecular and Cell Biology, National Institute of Molecular Biology and Biotechnology, National Science Complex, University of the Philippines Diliman, Philippines (December 2010 to April 2012)*

Peer- and/or Editor-Reviewed Journal Articles

1. Viaña JNM, Gilbert F (2018) 32 shades of neuroethics – a review of the Routledge Handbook of Neuroethics edited by L. Syd M Johnson and Karen S. Rommelfanger. The American Journal of Bioethics 18(10): W1-W3.
2. Viaña JNM, Carter A, Gilbert F (2018) Of meatballs and invasive neurotechnological trials: additional considerations for complex clinical decisions. AJOB Neuroscience 9(2): 100-104.
3. Viaña JNM, Gilbert F (2018) Deep brain stimulation for people with Alzheimer's disease: anticipating potential effects on the tripartite self. Dementia. Article first published online: March 11, 2018; https://doi.org/10.1177/1471301218761147
4. Viaña JNM, Illes J, Gilbert F (2018) Ethical considerations for cell implantation in Alzheimer's disease - selected abstracts from the 2017 International Neuroethics Society Annual Meeting. AJOB Neuroscience 9(1): W9-W10.
5. Gilbert F, Viaña JNM, Ineichen C (2018) Deflating the "DBS causes personality changes" bubble. Neuroethics. Article first published online: June 19, 2018; https://doi.org/10.1007/s12152-018-9373-8
6. Gilbert F, Viaña JNM (2018) A personal narrative on living and dealing with psychiatric symptoms after DBS surgery. Narrative Inquiry in Bioethics 8(1): 67-77.
7. Gilbert F, Viaña JNM, O'Connell CD, Dodds S (2018) Enthusiastic portrayal of 3D bioprinting in the media: ethical side effects. Bioethics 32(2): 94-102.
8. Viaña JNM, Bittlinger M, Gilbert F (2017) Ethical considerations for deep brain stimulation trials in patients with early-onset Alzheimer's disease. Journal of Alzheimer's Disease 58(2): 289-301.
9. Viaña JNM, Vickers JC, Cook MJ, Gilbert F (2017) Currents of memory: recent progress, translational challenges, and ethical considerations in fornix deep brain stimulation trials for Alzheimer's disease. Neurobiology of Aging 56: 202-210.
10. Viaña JNM, Bueno RJ, Gilbert F (2017) Beyond genomic association: ethical implications of elucidating disease mechanisms and genotype-influenced treatment response. The American Journal of Bioethics 17(4): 24-26.
11. Gilbert F, Goddard E, Viaña JNM, Carter A, Horne M (2017) I miss being me: phenomenological effects of deep brain stimulation. AJOB Neuroscience 8(2): 96-109.
12. Viaña JNM, Freitas L, Severo MC, Gilbert F (2016) Decoded neurofeedback: eligibility, applicability, and reliability issues for use in schizophrenia and major depressive disorder. AJOB Neuroscience 7(2): 127-129.

13. Viaña JNM, Gilbert F (2016) Big explanations for big expectations: deriving lessons from the Human Genome and Blue Brain Projects. AJOB Neuroscience 7(1): 18-20.
14. Gilbert F, Vranic A, Viaña JNM (2016) Acquired paedophilia and moral responsibility. AJOB Neuroscience 7(4): 209-11.
15. Luchicchi A, Bloem B, Viaña JNM, Mansvelder H, Role LW (2014) Illuminating the role of cholinergic signaling in circuits of attention and emotionally salient behaviors. Frontiers in Synaptic Neuroscience 6(24) doi: 10.3389/fnsyn.2014.00024.

Oral Presentations and Public Engagement

1. Viaña JNM, Gilbert F (2018) Stimulating the brain or altering the self? The effects of neurostimulation for Alzheimer's disease. Australasian Society for Philosophy and Psychology 2018 Meeting. Macquarie University, Sydney, Australia. 5-7 Dec.
2. Viaña JNM (2018) Ethics of research on novel medical technologies: from bench to bedside and beyond. National Institute of Molecular Biology and Biotechnology, College of Science, University of the Philippines Diliman, Quezon City, Philippines. 19 Nov.
3. Viaña JNM (2018) Clinical trials of invasive neurotechnologies for dementia: an Asian perspective. 19th Asian Bioethics Conference. Open University of Kaohsiung and Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Kaohsiung, Taiwan. 13-16 Nov.
4. Viaña JNM (2018) Genes, cells, and electrodes: ethical considerations for clinical trials on people with dementia. Health Ethics and Policy Laboratory Meeting. Department of Health Sciences & Technology (D-HEST), Swiss Federal Institute of Technology (ETH Zurich), Zurich, Switzerland. 23 Oct.
5. Viaña JNM (2018) Brain, cognition, person, and society: neuroethics of invasive interventions for Alzheimer's disease. Visiting Researchers' Presentation. Brocher Foundation, Hermance, Switzerland. 4 Oct.
6. Viaña JNM (2018) Alzheimer's disease: what do invasive neurotechnologies bring to the table? Visiting Researchers' Presentation. Brocher Foundation, Hermance, Switzerland. 4 Sept.
7. Viaña JNM (2018) Dementia, diversity, and resilience. European Forum Alpbach 2018. Congress Centrum Alpbach, Alpbach, Austria. 15-31 Aug.
8. Viaña JNM, Butaciu D, Ceylan M, Neuberg D, Ratheiser T, Röhrer B, Sowe A, Tracicaru R, Vu Dinh P (2018) Delving deeper into brain stimulation narratives: communicating ethical discourse through dance and verse choir. European Forum Alpbach 2018. Congress Centrum Alpbach, Alpbach, Austria. 15-31 Aug.
9. Viaña JNM (2018) Participation in invasive neurotechnological trials: considerations for a complex clinical decision. ARC (Australian Research Council Australian Centre) Centre of Excellence for Electromaterials Science Meeting, Hobart, Australia, 23 May.
10. Viaña JNM (2018) Participation in invasive neurotechnological trials: considerations for a complex clinical decision. ARC (Australian Research Council Australian Centre) Centre of Excellence for Electromaterials Science Ethics, Policy, and Public Engagement Team Meeting, Hobart, Australia, 7 May.
11. Viaña JNM, Gilbert F (2018) Men before mice: invasive brain stimulation trials for Alzheimer's disease. Herrenhausen Conference: Lost in the Maze? Navigating Evidence and Ethics in Translational Neuroscience. Herrenhausen Palace, Hanover, Germany, 14-16 Feb.
12. Viaña JNM (2018) Brain, mind, and society: neuroethical challenges in the 21st Century. Why? Symposium. Kellevie Mountain Bike Park, Kellevie, Australia. 9-11 Feb.

13. Viaña JNM (2018) Deep brain stimulation for people with Alzheimer's disease: Anticipating potential effects on the tripartite self. Neuroethics and Society Group Meeting. Monash Biomedical Imaging Auditorium, Monash University, Melbourne, Australia. 24 Jan.
14. Viaña JNM (2017) Invasive neurotechnologies for Alzheimer's disease: mapping the ethical landscape. Neuroscience and Society Group Meeting. Brain and Mental Health Laboratory, Monash University, Melbourne, Australia. 11 Dec.
15. Viaña JNM (2017) Currents of memory: the ethics of deep brain stimulation for Alzheimer's disease. Asia-Pacific Centre for Neuromodulation 2017 Deep Brain Stimulation Symposium. Queensland Brain Institute, University of Queensland, Brisbane, Australia. 24-25 Nov.
16. Viaña JNM (2017) Ethical issues in cell and gene therapy for Alzheimer's disease. Neuroethics Canada Meeting. Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, Canada. 30 Oct.
17. Viaña JNM (2017) The ethics of accessibility: why should we care? (Panel Discussion). UN Voices. TCoTA, Dechaineux Lecture Theatre, Hobart, Australia. 19 Apr.
18. Viaña JNM (2017) Neurobiological investigations: from molecules to society. Philippine Science High School – Western Visayas Campus, Iloilo City, Philippines, 4 Jan.
19. Viaña JNM (2016) Ethical considerations on the use of fornix deep brain stimulation for Alzheimer's disease. ARC (Australian Research Council Australian Centre) Centre of Excellence for Electromaterials Science Meeting, Hobart, Australia, 31 Aug.
20. Viaña JNM (2016) Ethical considerations on the use of deep brain stimulation and other invasive neurotechnologies for Alzheimer's disease. ARC (Australian Research Council Australian Centre) Centre of Excellence for Electromaterials Science Ethics, Policy, and Public Engagement Team Meeting, Hobart, Australia, 17 Aug.
21. Viaña JNM (2016) Neuroethics. Neurasmus 5th Annual Workshop, Budapest, Hungary, 11-14 Jul.
22. Gilbert F, Viaña JNM (2016) Enthusiastic portrayal of 3D bioprinting in the media: ethical side effects. 2016 Brocher Workshop, 3D Bioprinting: A New Medical and ethical Frontier? Geneva, Switzerland, 24-26 May.
23. Viaña JNM (2015) Role of dopaminergic projections from the ventral tegmental area to the medial prefrontal cortex during fear behaviour. Neurasmus 4th Annual Workshop. Vrije Universiteit Amsterdam, Amsterdam, Netherlands. 7-10 Jul.
24. Saloma CP, Viaña JNM (2013) Science, technology, and society - how biotechnology is touching our lives. College of Science Auditorium, National Science Complex, University of the Philippines Diliman, Quezon City, Philippines. 15 Feb.

Poster Presentations

1. Viaña JNM, Gilbert F (2018) Men before mice: invasive brain stimulation trials for Alzheimer's disease. Herrenhausen Conference: Lost in the Maze? Navigating Evidence and Ethics in Translational Neuroscience. Herrenhausen Palace, Hanover, Germany. 14-16 Feb.
2. Viaña JNM, Illes J, Gilbert F (2017) Ethical considerations for gene therapy in people with Alzheimer's disease. Neuroscience 2017 (Society for Neuroscience 2017 Annual Meeting). Walter E. Washington Convention Center, Washington, DC, USA. 11-15 Nov.
3. Viaña JNM, Illes J, Gilbert F (2017) Ethical considerations for cell implantation in Alzheimer's disease. International Neuroethics Society – 2017 Annual Meeting. American Association for the Advancement of Science Building, Washington, DC, USA. 9-10 Nov.

4. Viaña JNM (2017) Ethical considerations in patient selection and informed consent for Alzheimer's disease *in vivo* gene therapy trials. 2017 Sherwin B. Nuland Summer Institute in Bioethics (organized by the Yale Interdisciplinary Center for Bioethics) Student Poster Presentation. Medical Historical Library, Yale School of Medicine, New Haven, Connecticut, USA. 21 July.
5. Viaña JNM, Gilbert F (2016) Ethical implications of novel neurotechnologies for Alzheimer's disease. University of Tasmania 2016 Graduate Research Conference. University of Tasmania, Hobart, Australia. 1-2 Sep.
6. Viaña JNM, Vickers J, Gilbert F (2016) Ethical considerations for clinical trials of fornix DBS for patients with Alzheimer's disease. 10th FENS Forum of Neuroscience 2016. Copenhagen, Denmark. 2-6 Jul.
7. Viaña JNM, Gilbert F (2016) Ethical considerations for DBS in patients with early-onset autosomal dominant Alzheimer's disease. Neurizons 2016. Georg-August-Universität Göttingen, Göttingen, Germany. 31 May - 3 June.
8. Viaña JNM, Gilbert F, Blum A, Dodds S (2016) Enthusiastic portrayal of 3D bioprinting in the media. 11th Annual International Electromaterials Science Symposium. Deakin University, Melbourne, Australia. 10-12 Feb.
9. Luchicchi A, Viaña JNM, Mnie-Filali O, Pattij T, Mansvelder HD (2015) Labeling of afferent cholinergic projections to the rat medial prefrontal cortex using viral mediators. 9th International Brain Research Organization World Congress of Neuroscience. Rio de Janeiro, Brazil. 7-11 July.
10. Viaña JNM, Saloma CP (2012) Evaluation of sodium alginate as a 3D scaffold for neural precursor cell culture. 4th Outstanding Young Scientists Inc. (OYSI) Regional Symposium: Optimizing Coastal Resources for Equitable and Sustainable Development. Southeast Asian Fisheries Development Center, Iloilo, Philippines. 13-14 April.
11. Viaña JNM, Saloma CP (2012) Evaluation of sodium alginate as a 3D scaffold for neural precursor cell culture. 3rd National Convention of the Philippine Society for Cell Biology, Inc. (PSCB): Cell Biology at the Crossroads of Different Biological Disciplines. College of Science Auditorium, National Science Complex, University of the Philippines Diliman, Philippines. 18-19 Oct.

Awards, Grants, and Honours

Year	*Event and Sponsor or Award-Giving Body*	*Award/(s)*	*Total Amount (AUD)*
2018	Asian Bioethics Conference (Taiwan) - Asian Bioethics Association	Registration waiver (2,400 NTD); Awarded best oral presentation	110
2018	Fondation Brocher Residency (Switzerland) – Brocher Foundation	Scholarship for junior researchers: airfare (1,473 CHF), accommodation, and daily allowance (870 CHF)	3,327
2018	European Forum Alpbach (Austria) – European Alpbach Foundation	Registration waiver (1,400 EUR), accommodation (476 EUR), and meal allowance (289 EUR)	3,529
2018	Herrenhausen Conference (Germany) – Volkswagen Foundation	Return airfare from Hobart, Australia (~2,000 AUD), accommodation (387 EUR), travel insurance (13.20 EUR); Poster and oral presentations were selected among the top three	2,652
2017	International Neuroethics Society Meeting (USA)	Poster was selected by AJOB Neuroscience as one of the top posters	

2017	Sherwin B. Nuland Summer Institute in Bioethics, Yale University (USA) – Yale Interdisciplinary Center for Bioethics	Full tuition waiver (2,200 USD) from the Center and travel allowance (5,000 AUD) from the University of Tasmania	8,080
2016	Neurizons 2016 (Germany) and Federation of European Neuroscience Societies 2016 (Denmark) Conferences	Funding from the University of Tasmania to cover registration costs (499 AUD)	499
2015	PhD in Society and Culture at the University of Tasmania (Australia)	Full tuition waiver (98,000 AUD), Tasmanian Graduate Research Scholarship for 3 years (~78,000 AUD), and Overseas Student Health Cover (2,730 AUD)	178,730
2013	NEURASMUS Erasmus Mundus Master's Program in Neuroscience (France, Netherlands)	Category A scholarship: tuition waiver (16,000 EUR), living allowance (24,000 EUR), and mobility allowance (8,000 EUR); Graduated *mention assez bien*	78,240
2013	University of the Philippines Diliman (Philippines)	Certificate of Distinction (Parangal sa Mag-aaral) for achievement in a conference poster competition	
2012	3rd National Convention of the Philippine Society for Cell Biology, Inc. (Philippines)	Awarded best poster	
2012	Bachelor of Science in Molecular Biology and Biotechnology, University of the Philippines Diliman (Philippines)	Graduated *cum laude*	
2008	Secondary education at the Philippine Science High School, Western Visayas Campus (Philippines)	Research grant from Pfizer Inc. for a research project on bacterial bioremediation (20,000 PHP); Living allowance for 4 years (60,000 PHP); Graduated with high honours; awarded "Best in Filipino" and for "Outstanding Alumni Achievement	2,080
		TOTAL AMOUNT (AUD)	277,247

Additional Training: Seminars, Workshops, and Conferences

- Australasian Society for Philosophy and Psychology 2018 Meeting. Macquarie University, Sydney, Australia. 2018 Dec 5-7.
- 2018 International Mental Health Training Center Taiwan Conference: Experience of Mental Health Collaboration between Southeast Asia and Taiwan. Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Kaohsiung, Taiwan. 2018 Nov 14.
- 19th Asian Bioethics Conference. Open University of Kaohsiung and Kaohsiung Municipal Kai-Syuan Psychiatric Hospital, Kaohsiung, Taiwan. 2018 Nov 13-16.
- Herrenhausen Conference: Lost in the Maze? Navigating Evidence and Ethics in Translational Neuroscience. Herrenhausen Palace, Hanover, Germany. 2018 Feb 14-16.
- Why? Symposium. Kellevie Mountain Bike Park, Kellevie, Australia. 2018 Feb 9-11.

- Monash Dementia and Neurodegeneration Symposium. Monash Biomedical Imaging, Clayton, Australia. 2017 Nov 28.
- Asia-Pacific Centre for Neuromodulation 2017 Deep Brain Stimulation Symposium. Queensland Brain Institute, University of Queensland, Brisbane, Australia. 2017 Nov 24-25.
- Neuroscience 2017 (Society for Neuroscience 2017 Annual Meeting). Walter E. Washington Convention Center, Washington, DC, USA. 207 Nov 11-15.
- International Neuroethics Society – 2017 Annual Meeting. American Association for the Advancement of Science Building, Washington, DC, USA. 2017 Nov 9-10.
- Science Communication: The Crash Course. Organized by the Vancouver Coastal Health Research Institute. Blusson Spinal Cord Centre, Vancouver, Canada. 2018 Oct 18.
- University of Tasmania 2016 Graduate Research Conference. Hobart, Tasmania, Australia. 2016 Sep 1- 2.
- Neurasmus 5th Annual Workshop. Boscolo hotel, Budapest, Hungary; 2016 July 11-14.
- Federation of European Neuroscience Societies. 10th FENS Forum of Neuroscience. Bella Center, Copenhagen, Denmark; 2016 Jul 2 – 6.
- Federation of European Neuroscience Societies. Technical Workshop: Light that cures: therapies based on optogenetic manipulations and light-regulated drugs. Bella Center, Copenhagen, Denmark; 2016 Jul 2.
- Kick-off Meeting of the International Project "Psychiatric Neurosurgery - Ethical, Legal, and Societal Issues". Charité - Universitätsmedizin Berlin, Berlin, Germany; 2016 Jun 27-28.
- Neurizons 2016. Georg-August-Universität Göttingen, Göttingen, Germany. 2016 May 31 – June 3.
- Lake Geneva Graduate Conference (LG2C) 2016. University of Geneva, Geneva, Switzerland; 2016 May 27.
- 2016 Brocher Workshop. 3D Bioprinting: A New Medical and Ethical Frontier? Geneva, Switzerland; 2016 May 24-26.
- 11th Annual International Electromaterials Science Symposium. Deakin University, Melbourne, Australia; 2016 Feb 10-12.
- Dementia Intervention Symposium. Wicking Dementia Research and Education Centre. University of Tasmania Medical Sciences Building, Hobart, Tasmania, Australia; 2015 Dec 3.
- University of Tasmania 2015 Graduate Research Conference. Hobart, Tasmania, Australia. 2015 Sep 3 - 4.
- Neurasmus 4th Annual Workshop. VU University, Amsterdam, Netherlands; 2015 Jul 7 – 10.
- Bordeaux Neurocampus/ LabEx BRAIN symposium. University of Bordeaux, Talence, France; 2015 May 6.
- Federation of European Neuroscience Societies. 9th FENS Forum of Neuroscience. MiCo Congress Centre, Milan, Italy; 2014 Jul 5 – 9.
- Federation of European Neuroscience Societies. Technical Workshop: Epigenomic landscapes of the adult brain: implications in neuroplasticity and brain disorders. MiCo Congress Centre, Milan, Italy; 2014 Jul 5.
- Neurasmus 3rd Annual Workshop. Charité - Universitätsmedizin Berlin, Germany; 2014 Jul 10 - 15.
- Vrije Universiteit Medical Center. Brain Trees 2014 – a symposium on neural networks in cognition and disease. De Amstelzaal, VU University Medical Center, Amsterdam, Netherlands; 2014 Jun 23.
- Vrije Universiteit and Vrije Universiteit Medical Center Electron Microscopy Facility. Mini-symposium on correlative light electron and cryo-electron microscopy. Vrije Universiteit Amsterdam, De Boelelaan, Amsterdam, Netherlands; 2014 Jun 16.
- Donders Institute for Brain, Cognition and Behaviour. Synapsium 2014: Donders Cognitive Neuroscience Master Symposium. Radboud University Nijmegen, Netherlands; 2014 May 22.
- Neuroscience Campus Amsterdam. Annual Meeting 2014. Vrije Universiteit Amsterdam, De Boelelaan, Amsterdam, Netherlands; 2014 Apr 10.
- Amsterdam Animal Research Center. Advanced Rat Handling training course. Amsterdam Animal Research Center, Vrije Universiteit Amsterdam, De Boelelaan, Amsterdam, Netherlands; 2014 Mar 24.

- Neuroscience Campus Amsterdam. Symposium Valorisatie – a symposium on the valorization of science. Vrije Universiteit Amsterdam, De Boelelaan, Amsterdam, Netherlands; 2014 Jan 24.
- Philippine Genome Center. Bioinformatics Seminar for Health and Population Genomics Research – Conducting Genomic Research in the Era of Next-Generation Genotyping and Sequencing. National Institute of Molecular Biology and Biotechnology, National Science Complex, University of the Philippines Diliman, Quezon City, Philippines; 2013 Mar 20.
- GE Healthcare and University of the Philippines Diliman Multidimensional Imaging Center. Recent Advances in Cellular Technologies – a series of talks on stem cells and super-resolution cellular imaging and demonstration of fluorescence and time-lapse microscopy using the Delta Vision system. National Institute of Molecular Biology and Biotechnology and National Institute of Physics, College of Science Complex, University of the Philippines Diliman, Quezon City, Philippines; 2013 Mar 12.
- Laboratory Safety and Waste Management Seminar-Workshop. Institute of Chemistry, National Science Complex, University of the Philippines Diliman, Quezon City, Philippines. 2013 Feb 18.
- National Institute of Molecular Biology and Biotechnology 25th Anniversary Distinguished Lecture, Conference and Trade Fair. National Institute of Molecular Biology and Biotechnology, College of Science Complex, University of the Philippines Diliman, Quezon City, Philippines; 2012 Dec 11.
- 3rd National Convention of the Philippine Society for Cell Biology, Inc. (PSCB) National Convention: Cell Biology at the Crossroads of Different Biological Disciplines. College of Science Auditorium, National Science Complex, University of the Philippines Diliman, Philippines; 2012 Oct 18-19.
- Novartis Healthcare Philippines, Inc. Biocamp 2012: Novartis Biotechnology Leadership Camp. Theme: Staying Competitive in the Knowledge Economy. Asian Institute of Management Conference Center, Asian Institute of Management, Philippines; 2012 Jul 30.
- 4th Outstanding Young Scientists Inc. (OYSI) Regional Symposium: Optimizing Coastal Resources for Equitable and Sustainable Development. Southeast Asian Fisheries Development Center, Tigbauan, Iloilo, Philippines; 2012 Apr 14.

Student Supervision

As a University Research Associate at the University of the Philippines Diliman, I assisted the Project Investigator in supervising the following undergraduate students in their experiments and helped these students in defending their research projects and writing their thesis manuscripts:

- Alfonso HPH (2013) GspIx23 Turritoxin Recombinant Protein Production and Functional Assay in Mice
- Facun MAM (2013) Fabrication and Characterization of Alginate Scaffolds: Effect of Various Cross-linking Agents on 3D Neural Precursor Cell Culture
- Subosa JF (2013) Development of *In Vitro* and *In Vivo* Mouse Models for SWCNT-Immunoliposome-Mediated Hypothermia-Induced Tumor Reduction Therapy

English Proficiency

- Obtained an overall Academic IELTS band of 8.0 (Very Good User) and an overall TOEFL iBT score of 114/120

Honoraries, Societies, and Peer Review

Australasian Society for Philosophy and Psychology; Asian Bioethics Association; Society for Neuroscience; International Neuroethics Society; Neuroscience Bordeaux Association; Federation of European Neuroscience Societies; Dutch Neurofederation; Phi Kappa Phi International Honor Society; Phi Sigma Biological Sciences Honor Society; University of the Philippines Molecular Biology and Biotechnology Society; Scientia (official publication of the College of Science of the University of the Philippines Diliman; writer from 2008 to 2009)

Associate Editor, Journal of Alzheimer's Disease; Reviewer for Frontiers in Neuroscience, Journal of Parkinsonism and Restless Legs Syndrome, Clinical Interventions in Aging, and Frontiers in Clinical Drug Research - Alzheimer Disorders

Software

Windows, EndNote, Mendeley, SPSS, GraphPad Prism, Microsoft Office (Word, Excel, PowerPoint, OneNote, Publisher), Adobe (Acrobat, Illustrator, InDesign, PhotoShop), Cyberlink PowerDirector

Extra-curricular Activities

- *Online technological entrepreneurship class by Prof. Chuck Eesley from Stanford University (April to August 2012):* Together with teammates from Sweden, Russia, and the USA and under the mentorship of Prof. Reynaldo Garcia, conceptualized and developed a business plan for SciTree (http://scitree.org), an online networking platform that aims to connect scientists and potential investors or partners from companies/ industries
- *"Startup Boards: Advanced Entrepreneurship", an online class offered by Professor Clint Korver from Stanford University (October to December 2012):* Continued development and conceptualization of key features, such as complex systems analysis and technology landscaping, for SciTree (http://scitree.org)
- *Extramural language courses (Japanese 1, French 1, and French 2):* offered by the Department of Linguistics and Department of European Languages at the University of the Philippines Diliman (January 2011 to December 2012)

Referees

Lori Bruce, MA: Associate Director, Interdisciplinary Center for Bioethics; Director, Sherwin B. Nuland Summer Institute in Bioethics, Yale University, USA; Lori.Bruce@Yale.edu

Adrian Carter, PhD: Associate Professor (Research), School of Psychological Sciences and Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Australia; Adrian.Carter@monash.edu

Susan Dodds, PhD: Dean and Professor of Philosophy, School of Humanities & Languages, Faculty of Arts & Social Sciences, University of New South Wales, Australia; susan.dodds@unsw.edu.au

Frédéric Gilbert, **PhD**: ARC DECRA Fellow, Philosophy and Gender Studies Program, School of Humanities, University of Tasmania, Australia; fgilbert@utas.edu.au, fredericgilbertt@gmail.com

Judy Illes, PhD, FRSC, FCAHS: Professor of Neurology and Canada Research Chair in Neuroethics, Division of Neurology, Department of Medicine, University of British Columbia, Canada; jilles@mail.ubc.ca